

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
9 January 2003 (09.01.2003)

PCT

(10) International Publication Number
WO 03/002567 A1

(51) International Patent Classification⁷: **C07D 487/04**,
A61K 31/519, A61P 1/04

Boston, 35 Gatehouse Drive, Waltham, MA 02451 (US).
NGUYEN, Thanh [US/US]; 9092 Towne Centre Drive,
San Diego, CA 92121 (US).

(21) International Application Number: PCT/SE02/01303

(74) Agent: **GLOBAL INTELLECTUAL PROPERTY**; As-
traZeneca AB, S-151 85 Södertälje (SE).

(22) International Filing Date: 28 June 2002 (28.06.2002)

(25) Filing Language: English

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG,
SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ,
VN, YU, ZA, ZM, ZW.

(26) Publication Language: English

(30) Priority Data:
0102315-9 28 June 2001 (28.06.2001) SE

(71) Applicant (*for all designated States except US*): **AS-
TRAZENECA AB** [SE/SE]; S-151 85 Södertälje (SE).

(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR,
GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent
(BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,
NE, SN, TD, TG).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **BASARAB, Gre-
gory** [US/US]; AstraZeneca R & D Boston, 35 Gatehouse
Drive, Waltham, MA 02451 (US). **EYERMANN, Joseph**
[US/US]; AstraZeneca R & D Boston, 35 Gatehouse
Drive, Waltham, MA 02451 (US). **GOWRAVARAM,**
Madhusudhan [US/US]; AstraZeneca R & D Boston, 35
Gatehouse Drive, Waltham, MA 02451 (US). **GREEN,**
Oluyinka [US/US]; AstraZeneca R & D Boston, 35 Gate-
house Drive, Waltham, MA 02451 (US). **MACPHER-**
SON, Lawrence [US/US]; AstraZeneca R & D Boston,
35 Gatehouse Drive, Waltham, MA 02451 (US). **MORN-**
INGSTAR, Marshall [US/US]; AstraZeneca R & D

Published:

— with international search report

*For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.*

(54) Title: **NEW PYRAZOLO[3,4-D]PYRIMIDINES INHIBITING H. PYLORI INFECTIONS**

(57) Abstract: Compounds having the general formula , and pharmaceutical compositions containing them, and their use in the treatment or prophylaxis of *H. pylori* infection.

WO 03/002567 A1

NEW PYRAZOLO[3,4-D]PYRIMIDINES INHIBITING *H. PYLORI* INFECTIONS**Background**

Helicobacter pylori (*H. pylori*) is a highly motile, S-shaped, microaerophilic bacterium that colonizes in the gut. *H. pylori* infection is widespread with seroprevalence in the developed world between 30-60% (Everhart, 2000). Infection with the bacterium is usually contracted during childhood and patients remain infected for life unless treated. *H. pylori* infection has been shown to result in the development of gastritis, peptic ulcer, and mucosa-associated lymphoid tissue (MALT) lymphoma and has been linked to gastric adenocarcinoma (Go, 2000). Eradication of *H. pylori* infection is currently achieved using combination therapy of antimicrobial and antisecretory agents (Malfertheimer, 2000). However, compliance to these therapies is compromised due to adverse side effects and cumbersome dosing regimens. In addition, increasing prevalence of *H. pylori* strains resistant to existing antimicrobial therapies threatens to limit the use of these treatments (Qureshi, 2000; Graham, 2000). Given these considerations, an ideal therapy for *H. pylori* infection would be a novel (no existing resistance mechanisms), monotherapy antimicrobial that is selective for *H. pylori* eradication. The selectivity attribute is expected to aid in minimizing side effects due to gut sterilization.

H. pylori, like all Gram positive and Gram negative bacteria, utilize a cell wall comprised of crosslinked peptidoglycan units to maintain shape and resist high osmotic pressure potentials. Bacterial cell wall biosynthesis is a validated target for antimicrobial activity; cephalosporins, penicillins and glycopeptides are antimicrobial agents, which block cell wall biosynthesis (Walsh, 2000). Cell wall biosynthesis requires the enzyme MurI, a glutamate racemase, and therefore this enzyme is essential for bacterial viability (Doublet, 1993).

The present invention describes compounds, which specifically inhibit *H. pylori* MurI, compositions of such compounds and methods of use. The compounds disclosed herein represent a valuable contribution to the development of selective therapies directed to diseases resulting from *H. pylori* infection.

References

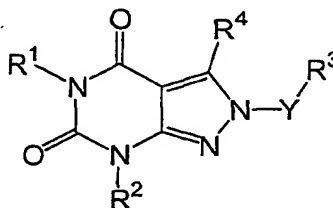
1. Doublet, P., et al., *The murI gene of Escherichia coli is an essential gene that encodes a glutamate racemase activity*. Journal of Bacteriology, 1993, 175(10): p. 2970-9.
2. Everhart, J.E., *Recent developments in the epidemiology of Helicobacter pylori*. Gastroenterology Clinics of North America, 2000, 29(3): p. 559-578.

- 2 -

3. Go, M.F. and D.T. Smoot, *Helicobacter pylori*, gastric MALT lymphoma, and adenocarcinoma of the stomach. *Seminars in Gastrointestinal Disease*, 2000, 11(3): p. 134-141.
4. Graham, D.Y., *Therapy of Helicobacter pylori: Current status and issues*. *Gastroenterology*, 2000, 118(2 SUPPL): p. S2-S8.
5. Malfertheiner, P., A. Leodolter, and U. Peitz, *Cure of Helicobacter pylori-associated ulcer disease through eradication*. *Bailliere's Best Practice and Research in Clinical Gastroenterology*, 2000, 14(1): p. 119-132.
6. Qureshi, W.A. and D.Y. Graham, *Antibiotic-resistant H. pylori infection and its treatment*. *Current Pharmaceutical Design*, 2000, 6(15): p. 1537-1544.
7. Walsh, C., *Molecular mechanisms that confer antibacterial resistance*. *Nature*, 2000, 406: p. 775-781.

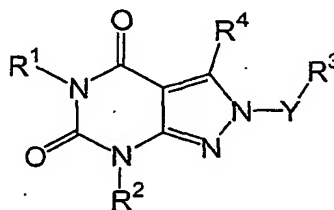
Summary of the Invention

The present invention relates to compounds having the general formula



and pharmaceutical compositions containing them, and their use in the treatment or prophylaxis of *H. pylori* infection. Also included herein are pharmaceutically acceptable salts of said compounds.

More specifically, compounds of the present invention have the formula:



(I)

R¹ is H, -OH, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted cycloalkynyl, optionally substituted aryl, optionally substituted alkoxy, amino, or optionally substituted heterocycle.

- 3 -

R² is H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted cycloalkynyl, optionally substituted aryl, optionally substituted alkoxy, amino, or optionally substituted heterocycle;

- 5 R³ is a monocyclic or bicyclic, saturated or unsaturated, ring system, which may contain from 5 to 12, preferably 5 to 10, ring atoms, 0, 1, 2 or 3 of which are heteroatoms independently selected from N, O, or S, the ring being substituted by 0, 1, 2 or 3 substituents selected from =O, halogen, -OR^a, C₁₋₆alkyl, C₁₋₆haloalkyl, -CN, nitro, -, -S(=O)_nR^c, -O(CH₂)_mHet, -O(CH₂)_mC(=O)Het, -O(CH₂)_mC(=O)NR^aR^a, -O(CH₂)_mC(=O)OR^a,
 10 -O(CH₂)_mNR^aR^a, -O(CH₂)_mOR^a, -S(CH₂)_mHet, -S(CH₂)_mC(=O)Het, -S(CH₂)_mC(=O)NR^aR^a, -S(CH₂)_mC(=O)OR^a, -S(CH₂)_mNR^aR^a, -S(CH₂)_mOR^a, -NHR^a, -NR^a₂, -NHC(=O)R^a, N=NR^a, aminocarbonyl, phenyl or benzyl; or R³ is represented by -Het, -Het-Het, R⁵, R⁵-Het, -Het-R⁵, -Het-O-R⁵, -phenyl-R⁵ or -phenyl-OR⁵.

- R⁴ is C₁₋₆alkyl, -NC₁₋₆alkyl, or -N(C₁₋₆alkyl)₂ wherein the C₁₋₆alkyl, -NC₁₋₆alkyl, -N(C₁₋₆alkyl)₂ are substituted by 0, 1 or 2 substituents selected from R^a, OR^a, halogen or phenyl provided however that R⁴ is not -(CH₂)_zCH₃, -(CH₂)_zCH₂OH, -(CH₂)_zCO₂H, or -(CH₂)_zCO₂C₁₋₆alkyl wherein z is 1, 2, 3, 4, 5, or 6.

- R⁴ may also be represented by -(CH₂)_nphenyl-Het, -(CH₂)_nR^d, -Het, -Het-Het, R⁵, -R⁵-Het, -Het-R⁵, -Het-O-R⁵, -phenyl-R⁵ or -phenyl-OR⁵ or a monocyclic or bicyclic, saturated or
 20 unsaturated, ring system, or a vicinal-fused derivative thereof, which may contain from 5 to 12, preferably 5 to 10, ring atoms, 0, 1, 2, 3 or 4 of which are heteroatoms independently selected from N, O, or S, the ring system being substituted by 0, 1, 2 or 3 substituents selected from B(OH)₂, vicinal -OCH₂CH₂O-, vicinal -OC₁₋₂haloalkylO-, vicinal -OCH₂O-, vicinal -CH₂OCH₂O-, =O, halogen, -R^bOR^a, -SR^a, -OR^a, C₁₋₆alkyl, C₁₋₆haloalkyl, -CN, -S(=O)_nR^c, -
 25 O(CH₂)_mHet, -O(CH₂)_mC(=O)Het, -O(CH₂)_mC(=O)NR^aR^a, -O(CH₂)_mC(=O)OR^a, -O(CH₂)_mNR^aR^a, -O(CH₂)_mOR^a, -S(CH₂)_mHet, -S(CH₂)_mC(=O)Het, -S(CH₂)_mC(=O)NR^aR^a, -S(CH₂)_mC(=O)OR^a, -S(CH₂)_mNR^aR^a, -S(CH₂)_mOR^a, -NHR^a, -NR^a₂, -NHC(=O)R^a, N=NR^a, NO₂, -C(=O)NR^aR^a, -C(=O)NR^aOR^a, -C(=O)NR^aR^bNR^aR^a, -C(=O)NR^aR^bOR^a, -C(=O)NR^aR^bS(=O)_nR^a, -C(=O)NR^aR^bHet, -C(=O)OR^a, -OC(=O)R^a, -C(=O)OR^bNR^aR^a, -
 30 C(=O)R^a, -C(=O)R^bNR^aR^a, -C(=NOR^a)R^a, -C(=NCN)R^a, -S(=O)₂NR^aR^a, -NR^aS(=O)₂R^a, -S(=O)₂NR^aR^bC(=O)NR^aR^a, -S(=O)₂NR^aR^bC(=O)OR^a, aminocarbonyl, phenyl or benzyl.

R⁵ is independently at each instance, phenyl substituted by 0, 1, 2, or 3 groups selected from halogen, C₁₋₆haloalkyl, -OC₁₋₆haloalkyl, C₁₋₆alkyl, -CN, nitro, -OH, -OR^c, -S(=O)_nR^c,

- 4 -

-O(CH₂)_mHet, -O(CH₂)_mC(=O)Het, -O(CH₂)_mC(=O)NR^aR^a, -O(CH₂)_mC(=O)OR^a,
 -O(CH₂)_mNR^aR^a, -O(CH₂)_mOR^a, -S(CH₂)_mHet, -S(CH₂)_mC(=O)Het, -S(CH₂)_mC(=O)NR^aR^a,
 -S(CH₂)_mC(=O)OR^a, -S(CH₂)_mNR^aR^a, -S(CH₂)_mOR^a, -R^bOR^a, -SR^a, -C(=O)NR^aR^a, -
 C(=O)NR^aOR^a, -C(=O)NR^aR^bNR^aR^a, -C(=O)NR^aR^bOR^a, -C(=O)NR^aR^bS(=O)_nR^a, -
 5 C(=O)NR^aR^bHet, -C(=O)OR^a, -OC(=O)R^a, -C(=O)OR^bNR^aR^a, -C(=O)R^a, -C(=O)R^bNR^aR^a, -
 C(=NOR^a)R^a, -C(=NCN)R^a, -S(=O)₂NR^aR^a, -NR^aS(=O)₂R^a, -S(=O)₂NR^aR^bC(=O)NR^aR^a, or -
 S(=O)₂NR^aR^bC(=O)OR^a.

R^a is, independently at each instance, H, C₁₋₆alkyl, -C(=O)C₁₋₄alkyl, C₁₋₄haloalkyl, -
 (CH₂)_q-, phenyl, benzyl, or 5 or 6-membered ring, saturated or unsaturated heterocycle
 10 containing 1, 2, 3, or 4 heteroatoms independently selected from N, O or S and wherein q is 0,
 1, 2, 3, 4, 5 or 6.

R^b is, independently at each instance C₁₋₆alkyl, -C(=O)C₁₋₄alkyl, C₁₋₄haloalkyl, -
 (CH₂)_q-, phenyl, benzyl, or 5 or 6-membered ring, saturated or unsaturated heterocycle
 containing 1, 2, 3, or 4 heteroatoms independently selected from N, O or S and wherein q is
 15 0, 1, 2, 3, 4, 5 or 6.

R^c is C₁₋₆alkyl, C₁₋₄haloalkyl, phenyl or benzyl.

R^d is phenyl substituted by 0, 1, 2 or 3 groups selected from -CN, halogen, nitro,
 C₁₋₆alkyl, C₁₋₄haloalkyl, -OH, -OR^c, -NR^aR^b, -S(=O)_nR^c, -C(=O)R^a, -S(=O)NR^aR^b,
 -C(=O)NR^aR^a, -C(=O)OR^a, -NR^aC(=O)R^a, -OC(=O)R^a, B(OH)₂, vicinal -OCH₂CH₂O-,
 20 vicinal -OC₁₋₂haloalkylO-, vicinal -OCH₂O-, vicinal -CH₂OCH₂O-, phenyl, benzyl or a 5- or
 6-membered ring, saturated or unsaturated heterocycle containing 1, 2, 3 or 4 heteroatoms
 independently selected from N, O, or S.

Y is CH₂, CHCH₃, S(=O) or S(=O)₂.

m is 1, 2 or 3.

25 n is 0, 1 or 2.

Het, unless otherwise defined, is a 5- or 6-membered ring, saturated or unsaturated
 heterocycle containing 1, 2, 3 or 4 heteroatoms independently selected from N, O, or S, and
 substituted by 0, 1, 2 or 3 substituents selected from halogen, -(CH₂)_nR^d C₁₋₄alkyl, -S(=O)_nR^c,
 -C(=O)R^a, or -S(=O)₂NR^aR^a vicinal -OCH₂CH₂O-, vicinal -OC₁₋₂haloalkylO-, vicinal
 30 -OCH₂O-, or vicinal -CH₂OCH₂O-, =O, halogen, cyano, -R^bOR^a, -R^bSR^a, -SR^a, -OR^a,
 C₁₋₆alkyl, C₁₋₄haloalkyl, -CN, nitro, -OH, -NHR^a, -NR^a₂, -NHC(=O)R^a, N=NR^a, -
 C(=O)NR^aR^a, -C(=O)NR^aOR^a, -C(=O)NR^aR^bNR^aR^a, -C(=O)NR^aR^bOR^a, -
 C(=O)NR^aR^bS(=O)_nR^a, -C(=O)NR^aR^bHet, -C(=O)OR^a, -OC(=O)R^a, -C(=O)OR^bNR^aR^a, -

- 5 -

$C(=O)R^bNR^aR^a$, $-C(=NOR^a)R^a$, $-C(=NCN)R^a$, $-NR^aS(=O)_2R^a$, $-S(=O)_2NR^aR^bC(=O)NR^aR^a$, $-S(=O)_2NR^aR^bC(=O)OR^a$.

Detailed Description

- 5 In a further aspect of the invention, R^1 may also be represented by C_{1-6} alkyl, wherein it is optionally substituted by 1 or 2 substituents selected from halogen, $-OR^a$, $-NR^aR^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-OC(=O)C_{1-4}$ alkyl or $-NR^aC(=O)C_{1-4}$ alkyl. In an additional embodiment, R^1 is Het- C_{1-3} alkyl-, $R^d-(CH_2)_n$ - or $-C_{1-6}$ alkyl that is substituted by 1 or 2 substituents selected from halogen, $-OR^a$, $-NR^aR^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$,
10 $-OC(=O)C_{1-4}$ alkyl or $-NR^aC(=O)C_{1-4}$ alkyl.

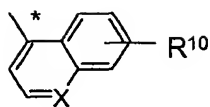
- When R^1 is represented by an optionally substituted alkyl it is preferably methyl or ethyl wherein the preferred substituent is an optionally substituted 5 or 6-membered heterocyclic ring. The heterocyclic rings may include for example thiophene, furan, pyrrole, triazole, diazole, imidazole, oxazole, thiazole, oxodiazole, isothiazole, isoxazole, thiadiazole,
15 pyridine, pyrimidine, pyrrolidine and pyrazine. The heterocyclic rings can be linked to the remainder of the molecule via any suitable carbon atom, or, when present, a nitrogen atom. The preferred heterocyclic rings include, but are not limited to, imidazole (preferably attached to a carbon atom on the ring), piperidine (preferably attached to the nitrogen atom on the ring), methylpiperidine (preferably attached to a carbon atom on the ring), morpholine
20 (preferably attached at the nitrogen).

In an additional embodiment, R^2 is $-C_{1-3}$ alkyl- $C(=O)R^a$; $-C_{1-3}$ alkyl- $C(=O)OR^a$; $-C_{1-3}$ alkyl- $C(=O)NR^aR^a$; $-C_{1-3}$ alkyl- $S(=O)_nR^c$; Het- C_{1-3} alkyl-; R^5 - C_{1-3} alkyl-; or C_{1-12} alkyl substituted with 0, 1, 2 or 3 substituents selected from $-OH$, halogen, $-CN$, $-OR^a$, $-NR^aR^a$ and $-SR^c$.

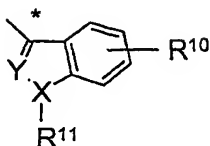
- 25 In a further embodiment, R^2 is Het- C_{1-3} alkyl-; R^5 - C_{1-3} alkyl-; C_{1-6} alkyl substituted with 0, 1 or 2 substituents selected from $-OH$, halogen, $-CN$, $-OR^a$, $-NR^aR^a$ and SR^c . In another aspect of the invention, R^2 is $-CH_2CH_2CH_3$, $-CH_2$ -cyclopropyl, $-CH_2CH(CH_3)_2$, $-CH_2CH_2CH_2F$, CH_2 -cyclobutyl, $-CH_2C(CH_3)_3$, $-CH_2CH_2CH(CH_3)_2$, $-CH_2CF_3$, $-CH_2$ -phenyl (preferably ortho substituted with $-CH_3$), $-CH_2$ -phenyl (preferably para substituted with $-OH$), CH_2 -isoxazolyl (preferably dimethyl), $-CH_2$ -S-phenyl, $-CH_2$ -phenylcarboxyl, or $-CH_2SCF_3$
30

In another aspect of the invention, R^3 is preferably represented by (* indicates the point of attachment to the Y group) formulas (i) or (ii):

- 6 -



(i)



(ii)

5 R^{11} is optionally substituted alkyl and optionally substituted $-S(=O)NR^aR^a$ and $S(=O)_n$, $n = 1$ or 2. X and Y are independently C, N, S or O provided that when R^4 is represented by
 10 Formula (i), X is not S or O and when R^4 is represented by Formula (ii) X and Y are not simultaneously C, S, or O, or X and Y are not S and O respectively or vice versa. R^{10} is, at any position on the bicyclic ring, H, optionally substituted C_{1-6} alkyl, halogen, -CN, nitro, $-CF_3$, or $-S(=O)_2CH_3$.

In an additional embodiment, R^3 is naphth-1-yl, quinolin-4-yl, indol-3-yl, indazol-3-yl,
 15 or benzothien-3-yl, any of which is substituted by 0, 1, 2 or 3 substituents selected from $-OR^a$, halogen and $-C_{1-4}$ alkyl, $-C_{1-4}$ haloalkyl.

In another aspect of the invention R^4 is $-(CH_2)_n$ phenyl, wherein the phenyl is substituted by 0, 1, 2 or 3 groups selected from -CN, nitro, C_{1-6} alkyl, halogen, C_{1-4} haloalkyl, -OH, $-OR^c$, $-NR^aR^a$, $-S(=O)_nR^c$, $-C(=O)NR^aR^a$, $-C(=O)OR^a$, $-NR^aC(=O)R^a$, $-OC(=O)R^a$,
 20 $B(OH)_2$, vicinal $-OCH_2CH_2O-$, vicinal $-OC_{1-2}$ haloalkylO-, vicinal $-OCH_2O-$, vicinal $-CH_2OCH_2O-$, phenyl or benzyl.

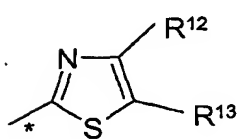
Additionally, R^4 is a saturated or unsaturated 5- or 6-membered heterocyclic ring, or a vicinal-fused benzo derivative thereof, containing 1, 2, 3 or 4 heteroatoms independently selected from N, O, or S, wherein the not more than one of the heteroatoms is S or O, and the
 25 ring is substituted by 0, 1 or 2 groups selected from -CN, nitro, C_{1-6} alkyl, C_{1-4} haloalkyl, -OH, $-OR^c$, $-NR^aR^a$, $-S(=O)_nR^c$, $-S(=O)_2NR^a$, $-C(=O)NR^aR^a$, $-C(=O)OR^a$, $-NR^aC(=O)R^a$, $-OC(=O)R^a$, $B(OH)_2$, vicinal $-OCH_2CH_2O-$, vicinal $-OC_{1-2}$ haloalkylO-, vicinal $-OCH_2O-$, vicinal $-CH_2OCH_2O-$, phenyl and benzyl.

- 7 -

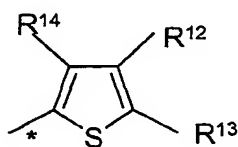
When R^4 is represented by a heterocyclic ring system having a vicinal fused derivative as defined above, it may be a vicinal fused benzo derivative thereof.

In another aspect of the invention, R^4 is represented by formulas a, b, c, d, e, f, g, h, i, j, k, l, m or n as follows (* indicates the point of attachment to the ring system):

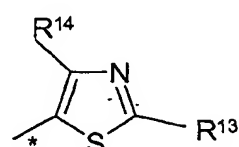
5



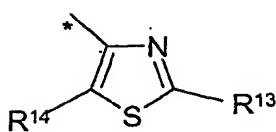
(a)



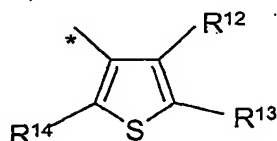
(b)



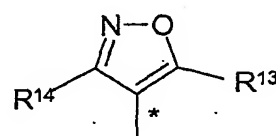
(c)



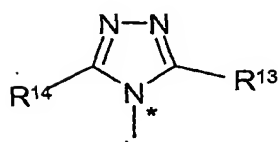
(d)



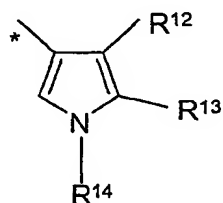
(e)



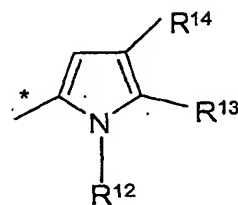
(f)



(g)



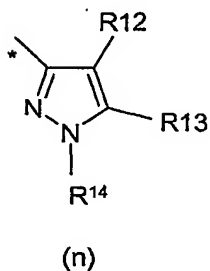
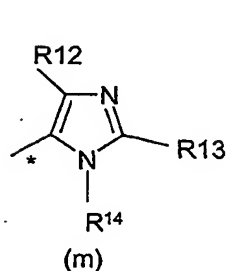
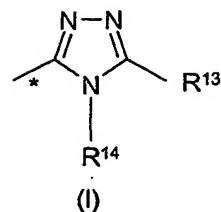
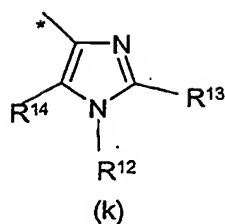
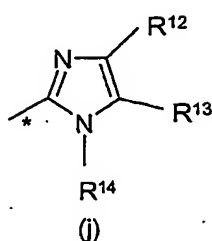
(h)



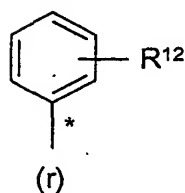
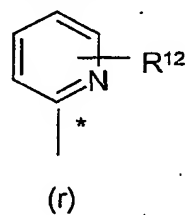
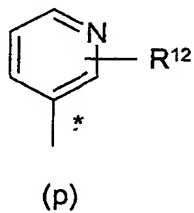
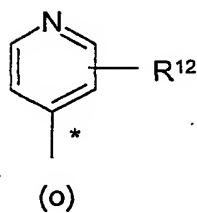
(i)

10

- 8 -



In another aspect of the invention, R^4 may additionally be represented by formulas o-r as follows (* indicates the point of attachment to the ring system):



wherein R^{12} , R^{13} and R^{14} are each independently represented by H, C_{1-6} alkyl, -CN, $-NR^aR^a$, -
 10 nitro, $-C(=O)R^a$, $-C(=O)NR^a$, $-C(=O)NR^aR^a$, $-C(=O)NR^aS(=O)_2R^a$, $-C(=O)NR^a$ -Het, -
 $C(=O)NR^aN$, $-C(=O)NR^aNR^a$, $-C(=O)NR^aR^bNR^a$, $-C(=O)NR^aR^bNR^aR^a$, $-C(=O)NR^aR^bOR^a$, -
 $C(=O)NR^aR^bS(=O)_2R^a$, $-C(=O)NR^aR^b$ -Het, $-C(=O)NR^aO$, $-C(=O)NR^aOR^a$, $-C(=O)NOR^a$, -
 $C(=O)R^bNR^a$, $-C(=O)R^aN_2R^a$, $-C(=O)R^bNR^aR^a$, $-C(NOR^a)R^a$, $-C(=NCN)R^a$, $-C(=O)OR^a$, -
 $C(=O)OR^bNR^a$, $-C(=O)OR^bNR^aR^a$, $-C(=O)R^a$, $-C(=O)OR^bNR^aR^a$, $-OC(=O)R^a$, $-C(=O)R^a$.

- 9 -

SR^a, =S, -NC(=O)R^a, -NC(=O)OR^a, -NS(=O)₂ R^aR^b, -NR^bS(=O)₂ R^a, C(=NO)R^a -C(=NOR^a)R^a, -S(=O)₂ R^a, -S(=O)₂N R^a, -S(=O)₂NR^aR^a, -S(=O)₂NR^b C(=O)NR^aR^a, -S(=O)₂NR^aR^b C(=O)OR^a, -S(=O)₂NR^a C(=O)O-, and -C(=NCN) R^a.

In an additional embodiment for formulas b-e, h, j, l, m, and n, when R¹², R¹³ or R¹⁴ is a 5-, or 6-membered saturated or unsaturated ring, it is preferably a piperazine, pyridine, tetrazole, imidazole, or morpholine ring.

In formulas a-n, when R¹⁴ is represented C₁₋₆alkyl, it is preferably represented by methyl, ethyl, propyl, butyl, isopropyl, and isobutyl, most preferably methyl.

In formula b, R¹² and R¹³ are preferably represented by H and R¹⁴ is preferably represented by C₁₋₆alkyl, preferably, methyl, ethyl, propyl, butyl, isopropyl, isobutyl, or *t*-butyl.

When R¹² or R¹³ is represented by -C(=O)R^a, -C(=O)O R^a, -C(O) R^a, -S R^a, S(=O) R^a, -C(=O)N R^a, -C(=O)NO R^a, -NC(=O) R^a, R^a is preferably C₁₋₆alkyl, most preferably, methyl, ethyl, butyl, isopropyl, cyclopropyl, or isobutyl.

When the expression "optionally substituted" is used above, it is meant that the substituent referred to is optionally substituted and the substituent is preferably selected from halogen, nitro, cyano, hydroxy, trifluoromethyl, amino, carboxy, carboxamido, amidino, carbamoyl, mercapto, sulfamoyl, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ alkoxy, C_{1b-4} alkanoyl, C₁₋₄ alkanoyloxy, N-(C₁₋₄ alkyl), N(C₁₋₄ alkyl)₂, C₁₋₄ alkanoylamino, (C₁₋₄ alkanoyl)₂amino, N-(C₁₋₄ alkyl)carbamoyl, N,N-(C₁₋₄ alkyl)₂carbamoyl, (C₁₋₄)S, (C₁₋₄ alkyl)S(O), (C₁₋₄alkyl)S(O)₂, (C₁₋₄) alkoxycarbonyl, N-(C₁₋₄ alkyl)sulfamoyl, N,N-C₁₋₄ alkyl)sulfamoyl, C₁₋₄ alkylsulfonfylamino, phenyl, and heterocyclic.

The term "hydrocarbyl" refers to any structure comprising only carbon and hydrogen atoms up to 14 carbon atoms.

The term "alkyl" used alone or as a suffix or prefix, refers to straight or branched chain hydrocarbyl radicals comprising 1 to about 12 carbon atoms.

The term "alkenyl" refers to straight or branched chain hydrocarbyl radicals having at least one carbon-carbon double bond and comprising at least 2 up to about 12 carbon atoms.

The term "alkynyl" refers to straight or branched chain hydrocarbyl radicals having at least one carbon-carbon triple bond and comprising at least 2 up to about 12 carbon atoms.

The term "cycloalkyl" refers to ring-containing hydrocarbyl radicals comprising at least 3 up to about 12 carbon atoms.

- 10 -

The term "cycloalkenyl" refers to ring-containing hydrocarbyl radicals having at least one carbon-carbon double bond and comprising at least 3 up to about 12 carbon atoms.

The term "cycloalkynyl" refers to ring-containing hydrocarbyl radicals having at least one carbon-carbon triple bond and comprising about 7 up to about 12 carbon atoms.

5 The term "aromatic" refers to hydrocarbyl radicals having one or more polyunsaturated carbon rings having aromatic character, (*e.g.*, $4n + 2$ delocalized electrons) and comprising 6 up to about 14 carbon atoms.

The term "aryl" refers to aromatic radicals including both monocyclic aromatic radicals comprising 6 carbon atoms and polycyclic aromatic radicals comprising up to about
10 14 carbon atoms.

The term "alkylene" refers to divalent alkyl moieties, wherein said moiety serves to link two structures together.

The term "heterocycle", "heterocyclic" or "heterocyclyl" refers to ring-containing monovalent and divalent radicals having one or more heteroatoms, independently selected
15 from N, O and S, as part of the ring structure and comprising at least 3 and up to about 20 atoms in the rings preferably 5 and 6 membered rings. Heterocyclic moieties may be saturated or unsaturated, containing one or more double bonds, and heterocyclic moieties may contain more than one ring.

The term "heteroaryl" refers to heterocyclic monovalent and divalent radicals having
20 aromatic character.

Heterocyclic, heterocycle or heterocyclyl compounds include for example monocyclic moieties such as: aziridine, oxirane, thiirane, azetidine, oxetane, thietane, pyrrolidine, pyrroline, imidazolidine, pyrazolidine, dioxolane, sulfolane, 2,3-dihydrofuran, 2,5-dihydrofuran, tetrahydrofuran, thiophane, piperidine, 1,2,3,6-tetrahydro-pyridine, piperazine,
25 morpholine, thiomorpholine, pyran, thiopyran, 2,3-dihydropyran, tetrahydropyran, 1,4-dihydropyridine, 1,4-dioxane, 1,3-dioxane, dioxane, homopiperidine, 2,3,4,7-tetrahydro-1*H*-azepine, homopiperazine, 1,3-dioxepane, 4,7-dihydro-1,3-dioxepin, and hexamethylene oxide. In addition heterocyclic moieties include heteroaryl rings such as: pyridine, , pyrazine, pyrimidine, pyridazine, thiene, furanl, pyrrole, imidazole, thiazole, oxazole, pyrazole,
30 isothiazole, isoxazole, 1,2,3-triazole, tetrazolel, 1,2,3-thiadiazole, 1,2,3-oxadiazole, 1,2,4-triazole, 1,2,4-thiadiazole, 1,2,4-oxadiazole, 1,3,4-triazole, 1,3,4-thiadiazole, and 1,3,4-oxadiazole. Additionally, heterocyclic moieties encompass polycyclic moieties such as: indazole, indole, indoline, quinoline, tetrahydroquinoline, isoquinoline,

- 11 -

tetrahydroisoquinoline, 1,4-benzodioxan, coumarin, dihydrocoumarin, benzofuran, 2,3-dihydrobenzofuran, 1,2-benzisoxazole, benzothiophene, benzoxazole, benzthiazole, benzimidazole, benztriazole, thioxanthine, carbazole, carboline, acridine, pyrrolizidine, and quinolizidine.

5 In addition to the polycyclic heterocycles described above, heterocyclic or heterocycle compounds include polycyclic heterocyclic moieties wherein the ring fusion between two or more rings comprises more than one bond common to both rings and more than two atoms common to both rings. Examples of such bridged heterocycles include quinuclidine, diazabicyclo[2.2.1]heptane and 7-oxabicyclo[2.2.1]heptane.

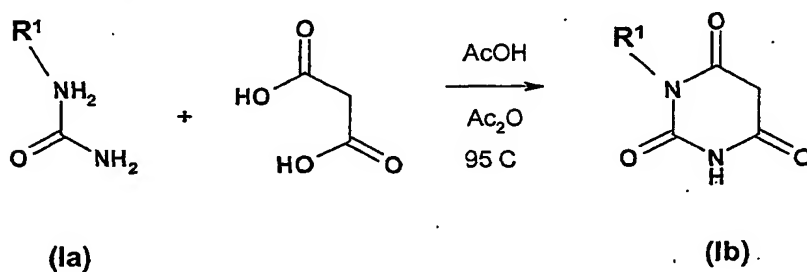
10 The term "halo" or "halogen" refers to fluorine, chlorine, bromine and iodine radicals.

The term "alkoxy" refers to radicals of the general formula $-O-R$, wherein R is selected from a hydrocarbyl radical. Examples of alkoxy moieties include methoxy, ethoxy, propoxy, isopropoxy, butoxy, t-butoxy, isobutoxy, cyclopropylmethoxy, allyloxy, and propargyloxy.

15 The term amine or amino refers to radicals of the general formula $-NRR'$, wherein R and R' are independently selected from hydrogen or a hydrocarbyl radical.

Processes for making compounds of formula 1 are provided as further embodiments of the invention. Also provided are novel intermediates represented by formulas, Ia, Ib, Ic, Id, Ie, and If.

20 In an aspect of the invention, intermediate compounds of formula Ib may be formed by reacting a compound of formula Ia with a dicarboxylic acid, acetic anhydride and acetic acid mixing with heat for about 3 hours and then cooled:



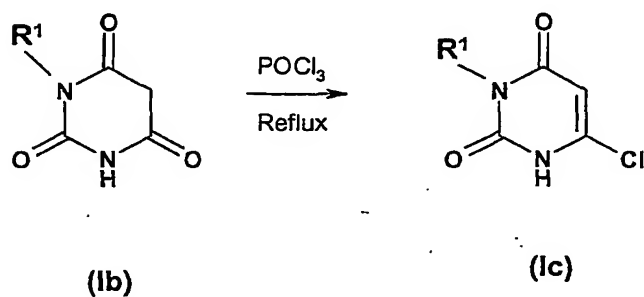
25

Unless otherwise specified or defined, R^1, R^2, R^3, R^4 are as defined above.

Intermediate Ic may be formed by for example reacting a compound of Ib with for example a

- 12 -

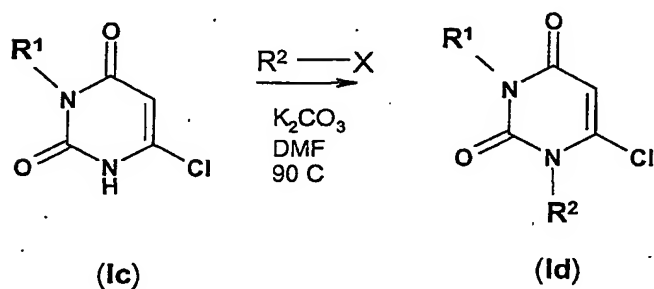
chlorinating compound such as phosphorous oxychloride, sometimes with small amounts of water and refluxed for about an hour and then cooled:



5

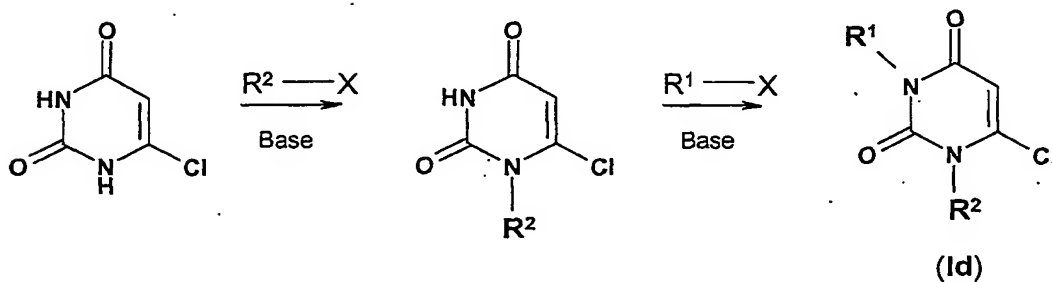
Intermediate **Id** may be formed by reacting a compound of formula **Ic** with R^2-X in a solvent such as DMF and a base such as K_2CO_3 , with heat as set forth below:

10



Intermediate **Id** also can be synthesized by using an alternate approach as shown below.

15

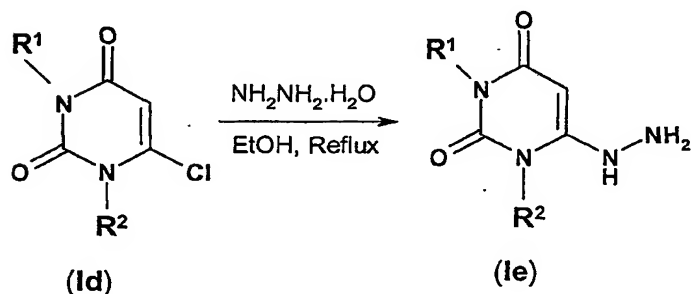


- 13 -

wherein X is a leaving group such as a halogen, mesylate, or tosylate.

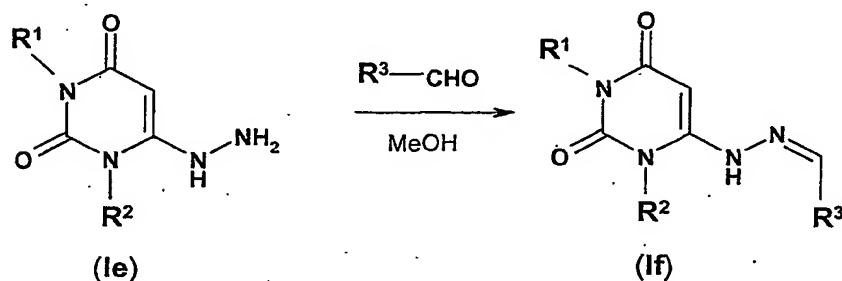
An intermediate compound of formula **Ie** may be formed by reacting a compound of Formula **Id** with $\text{NH}_2\text{NH}_2\cdot\text{H}_2\text{O}$ in a solvent such as ethanol and refluxed as follows:

5



10

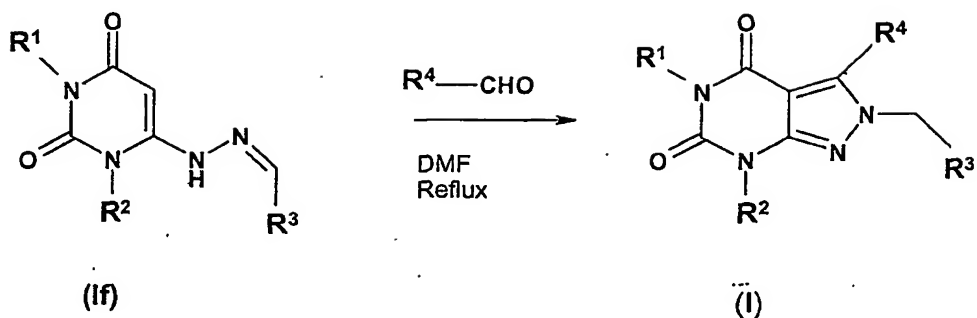
Intermediate compound of Formula **If** may be formed by reacting a compound of formula **Ie** with $\text{R}^3\text{-CHO}$ in a solvent such as Methanol as follows:



In another aspect of the invention, compounds of formula **I** may be formed by reaction of compounds of formula **If** with $\text{R}^4\text{-CHO}$ in a polar protic or aprotic solvent such as DMF, DMSO, ethanol or acetic acid. The conversion of **If** to a compound of the present invention, represented by formula **II**, may be accelerated by addition of an amine catalyst such as piperidine or triethylamine, or a salt catalyst such as piperidinium acetate or sodium acetate. Reaction temperatures may range between 60 °C and 180 °C.

20

- 14 -

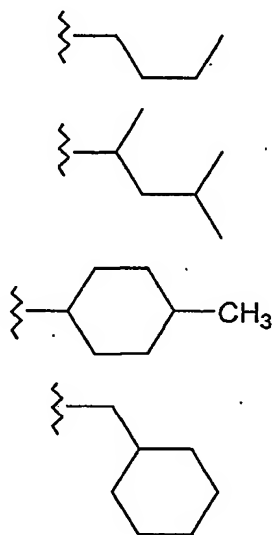


Another aspect of the invention involves the manufacture of a medicament for the treatment or prophylaxis of *H. pylori* infection comprising a compound included in any of the above embodiments.

5 Another aspect of the invention involves the use of a compound included in any of the above embodiments for the treatment or prophylaxis of *H. pylori* infection.

Another aspect of the invention involves a pharmaceutical composition for the treatment or prophylaxis of *H. pylori* infection, comprising: a therapeutically-effective amount of a compound included in any of the above embodiments; and a pharmaceutically-
 10 acceptable diluent or carrier.

Particular compounds of this invention are provided as the Examples herein below. C_Y-alkyl, unless otherwise specified, means an alkyl chain containing a minimum Y total carbon atoms and a maximum Z total carbon atoms. These alkyl chains may be branched or unbranched, cyclic, acyclic or a combination of cyclic and acyclic. For example, the
 15 following substituents would be included in the general description "C₄₋₇-alkyl":



- 15 -

Cy-zhaloalkyl, unless otherwise specified, means an alkyl group, as described above, wherein any number of the hydrogen atoms usually present on the alkyl are replaced with halogen atoms.

Pharmaceutically-acceptable salts may be prepared from the corresponding acid in conventional manner. Non-pharmaceutically-acceptable salts may be useful as intermediates and as such are another aspect of the present invention.

The term "oxo" means a double bonded oxygen (=O).

Some of the compounds of the present invention are capable of forming salts with various inorganic and organic acids and bases and such salts are also within the scope of this invention. Examples of such acid addition salts include acetate, adipate, ascorbate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, citrate, cyclohexyl sulfamate, ethanesulfonate, fumarate, glutamate, glycolate, hemisulfate, 2-hydroxyethyl-sulfonate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, hydroxymaleate, lactate, malate, maleate, methanesulfonate, 2-naphthalenesulfonate, nitrate, oxalate, pamoate, persulfate, phenylacetate, phosphate, picrate, pivalate, propionate, quinate, salicylate, stearate, succinate, sulfamate, sulfanilate, sulfate, tartrate, tosylate (p-toluenesulfonate), trifluoroacetate, and undecanoate. Base salts include ammonium salts, alkali metal salts such as sodium, lithium and potassium salts, alkaline earth metal salts such as aluminum, calcium and magnesium salts, salts with organic bases such as dicyclohexylamine salts, N-methyl-D-glucamine, and salts with amino acids such as arginine, lysine, ornithine, and so forth. Also, basic nitrogen-containing groups may be quaternized with such agents as: lower alkyl halides, such as methyl, ethyl, propyl, and butyl halides; dialkyl sulfates like dimethyl, diethyl, dibutyl; diamyl sulfates; long chain halides such as decyl, lauryl, myristyl and stearyl halides; aralkyl halides like benzyl bromide and others. Non-toxic physiologically-acceptable salts are preferred, although other salts are also useful, such as in isolating or purifying the product.

The salts may be formed by conventional means, such as by reacting the free base form of the product with one or more equivalents of the appropriate acid in a solvent or medium in which the salt is insoluble, or in a solvent such as water, which is removed *in vacuo* or by freeze drying or by exchanging the anions of an existing salt for another anion on a suitable ion-exchange resin.

In order to use a compound of the formula (I) or a pharmaceutically acceptable salt thereof for the therapeutic treatment (including prophylactic treatment) of mammals including

- 16 -

humans, it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Therefore in another aspect the present invention provides a pharmaceutical composition, which comprises a compound of the formula (I) or a pharmaceutically acceptable salt and pharmaceutically acceptable carrier.

The pharmaceutical compositions of this invention may be administered in a standard manner for the disease condition that it is desired to treat, for example by oral, topical, parenteral, buccal, nasal, vaginal or rectal administration or by inhalation or insufflation. For these purposes the compounds of this invention may be formulated by means known in the art into the form of, for example, tablets, capsules, aqueous or oily solutions, suspensions, emulsions, creams, ointments, gels, nasal sprays, suppositories, finely divided powders or aerosols or nebulisers for inhalation, and for parenteral use (including intravenous, intramuscular or infusion) sterile aqueous or oily solutions or suspensions or sterile emulsions.

In addition to the compounds of the present invention, the pharmaceutical composition of this invention may also contain, or be co-administered (simultaneously or sequentially) with, one or more pharmacological agents of value in treating one or more disease conditions referred to herein.

The pharmaceutical compositions of this invention will normally be administered to humans so that, for example, a daily dose of 0.01 to 25 mg/kg body weight (and preferably of 0.1 to 5 mg/kg body weight) is received. This daily dose may be given in divided doses as necessary, the precise amount of the compound received and the route of administration depending on the weight, age and sex of the patient being treated and on the particular disease condition being treated according to principles known in the art.

Typically unit dosage forms will contain about 1 mg to 500 mg of a compound of this invention. For example a tablet or capsule for oral administration may conveniently contain up to 250 mg (and typically 5 to 100 mg) of a compound of the formula (I) or a pharmaceutically acceptable salt thereof. In another example, for administration by inhalation, a compound of the formula (I) or a pharmaceutically acceptable salt thereof may be administered in a daily dosage range of 5 to 100 mg, in a single dose or divided into two to four daily doses. In a further example, for administration by intravenous or intramuscular injection or infusion, a sterile solution or suspension containing up to 10% w/w (and typically

- 17 -

5% w/w) of a compound of the formula (I) or a pharmaceutically acceptable salt thereof may be used.

The compounds of the formula (I) and their pharmaceutically acceptable salts may be made by processes as described and exemplified herein and by processes similar thereto and by processes known in the chemical art. If not commercially available, starting materials for these processes may be made by procedures, which are selected from the chemical art using techniques which are similar or analogous to the synthesis of known compounds.

Some individual compounds within the scope of this invention may contain double bonds. Representations of double bonds in this invention are meant to include both the E and the Z isomer of the double bond. Additionally, some species within the scope of this invention may contain one or more asymmetric centers. This invention includes the use of any of the optically pure stereoisomers as well as any combination of stereoisomers.

The following biological test methods, data and Examples serve to illustrate and further describe the invention.

The utility of a compound of the invention or a pharmaceutically acceptable salt thereof (hereinafter, collectively referred to as a "compound") may be demonstrated by standard tests and clinical studies, including those disclosed in the publications described below.

20 Glutamate Racemase Activity Assay:

Glutamate racemase (MurI) activity was assayed by measuring the conversion of glutamate from D to L enantiomer. This reaction was coupled to the reduction of NAD⁺ to NADH by L-glutamate dehydrogenase (LGDH). LGDH from bovine liver was obtained as a lyophilized powder (Sigma #G-7882) and dissolved in 10 mM Tris (Sigma #T-6791), pH 7.5, buffer containing 0.1 mM EDTA (Fisher #BP118-500) and 50% glycerol (Sigma #G-9012). The assay mixture consisted of 100 mM Tris-HCl, pH 8.0, 10 mM β -NAD (Sigma #N-7004), 5 mM DTT (Sigma #D-5545), 0.03% PEG (mw 8000, Sigma #P-5413), 0.03 mg/mL BSA (Pierce #23210), 15 U/mL LGDH, D-glutamate (Fluka #49460), and purified MurI. The following MurI concentrations were used: 1000 nM *H. pylori* MurI, 0.7 nM *E. faecalis* MurI, or 0.4 nM *E. coli* MurI. In the case of *E. coli* MurI 14 μ M UDP-MurNAc-Ala was also added. The final concentration of D-glutamate added for *H. pylori* MurI was 40 μ M, and the other orthologs used 1 mM D-glutamate. The assay was performed in 96-well black microtiter plates (Greiner #XN2-9511) with a final assay volume of 100 μ L. Compounds were prepared

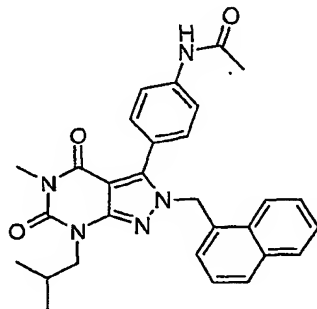
- 19 -

- (x) Mass spectra (MS) were run using an automated system with atmospheric pressure electrospray ionization (ESI). Generally, only spectra where parent masses are observed are reported. The lowest mass major ion is reported for molecules where isotope splitting results in multiple mass spectral peaks (for example when chlorine is present).
- 5 Terms and abbreviations: solvent mixture compositions are given as volume percentages or volume ratios. In cases where the NMR spectra are complex, only diagnostic signals are reported. atm = atmospheric pressure, Boc = t-butoxycarbonyl, Cbz = benzyloxycarbonyl, DCM = methylene chloride, DIPEA = diisopropylethylamine, DMF = N,N-dimethylformamide, DMSO = dimethyl sulfoxide, Et₂O = diethyl ether, EtOAc = ethyl acetate, equiv. =
- 10 equivalent(s), h = hour(s), HPLC = high performance liquid chromatography, min = minutes, NMR = nuclear magnetic resonance, psi = pounds per square inch, TFA = trifluoroacetic acid, THF = tetrahydrofuran.

15 Example 1

N-{4-[7-isobutyl-5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]phenyl}acetamide

20



(a) 1-Methylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione

- Acetic anhydride (34 ml) was added to a solution of malonic acid (20 g) and methylurea (12.5
- 25 g) in acetic acid (46 ml). The mixture was heated to 95°C for 3 hours then cooled to room temperature. The resulting solution was concentrated under reduced pressure and the residue

- 18 -

as 20 mM stock solutions in dimethyl sulphoxide (DMSO, Sigma #D-5879) and serial dilutions were prepared from these solutions using DMSO, 2 μ L of which were added to the wells. Activity at room temperature was measured by monitoring the increase in fluorescence using a TECAN Ultra platereader with 340 nm excitation and 465 nm emission filters. The compounds provided have measured IC₅₀ of less than 400 μ M

The expression use in the below examples "was made following the procedure describe above" refers generally the to process steps above and other examples where necessary.

Examples

- 10 The invention will now be illustrated by the following non-limiting examples, in which, unless stated otherwise:
- (i) temperatures are given in degrees Celsius ($^{\circ}$ C); unless otherwise stated, operations were carried out at room or ambient temperature, that is, at a temperature in the range of 18-25 $^{\circ}$ C;
 - 15 (ii) organic solutions were dried over anhydrous magnesium sulfate or sodium sulfate; evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 Pascals; 4.5-30 mm Hg) with a bath temperature of up to 60 $^{\circ}$ C;
 - (iii) chromatography means flash chromatography on silica gel; thin layer chromatography (TLC) was carried out on silica gel plates;
 - 20 (iv) in general, the course of reactions was followed by TLC or analytical HPLC and reaction times are given for illustration only;
 - (v) melting points are uncorrected and (dec) indicates decomposition;
 - (vi) final products had satisfactory proton nuclear magnetic resonance (NMR) spectra;
 - (vii) when given, NMR data is in the form of delta values for major diagnostic protons,
 - 25 given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, determined at 500 MHz using deuterated chloroform (CDCl_3) or $\text{DMSO}-d_6/\text{CD}_3\text{OD}$ as solvent; conventional abbreviations for signal shape are used; for AB spectra the directly observed shifts are reported; coupling constants (J) are given in Hz; Ar designates an aromatic proton when such an assignment is made;
 - 30 (viii) reduced pressures are given as absolute pressures in pascals (Pa); elevated pressures are given as gauge pressures in bars;
 - (ix) solvent ratios are given in volume:volume (v/v) terms; and

- 20 -

was taken into ethanol (50 ml) and stirred vigorously. The precipitated solid was filtered and washed with ether. The solid was recrystallized in warm water to give the sub-title compound (6.6 g) as a solid. Mass: 140.91 (M-H).

5 **(b) 6-Chloro-3-methylpyrimidine-2,4[1H,3H]-dione**

1-Methylpyrimidine-2,4,6(1H,3H,5H)-trione (3 g) was suspended in phosphorus oxychloride (70 ml). Water (0.6 ml) was added and the mixture was heated at reflux for 1 hour. The reaction was allowed to cool and was then concentrated under reduced pressure. The residue was poured onto a mixture of ice and water (60 ml). The precipitated solid was collected,
10 washed with water and dried to give the sub-title compound (2.2 g). Mass: 158.87 (M-H).

(c) 6-Chloro-1-isobutyl-3-methylpyrimidine-2,4(1H,3H)-dione

3-Iodo-2-methylpropane (4.6 g) and potassium carbonate (8.62 g) were added to a solution of 6-Chloro-3-methylpyrimidine-2,4[1H,3H]-dione (2.0 g) in dimethylformamide (10 ml). The
15 mixture was heated at 90°C for 18 hours then cooled to room temperature. The solution was diluted with 5% aqueous HCl solution until solution becomes acidic and extracted twice with diethyl ether. The combined organic extracts were dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure. The residue was purified by column chromatography over silica eluting with hexanes : ethyl acetate (1:1) to give the subtitle
20 compound (1.5 g).
Mass: 216.88 (M+H).

(d) 6-Hydrazino-1-isobutyl-3-methylpyrimidine-2,4(1H,3H)-dione

Hydrazine hydrate (6.5 ml) was added to a solution of 6-Chloro-1-isobutyl-3-
25 methylpyrimidine-2,4(1H,3H)-dione (10 g) in ethanol (40 ml). The mixture was heated at reflux for 5 hours, cooled to room temperature and then evaporated under reduced pressure. The residue was crystallized from ethanol to give the subtitle compound (6.7 g). Mass: 213.00 (M+H).

30 **(e) 1-naphthaldehyde (3-isobutyl-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)hydrazone**

- 21 -

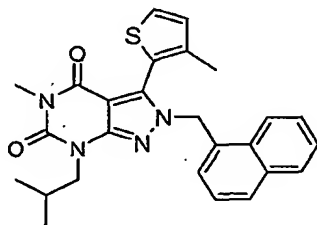
6-Hydrazino-1-isobutyl-3-methylpyrimidine-2,4(1*H*,3*H*)-dione (1 g) was dissolved in warm methanol (40 ml) and treated with 1-naphthaldehyde (0.78 g). After 2 hours, the precipitated solid was filtered and dried to give the subtitle compound (1.5 g). Mass: 350.96 (M+H).

5 (f) *N*-{4-[7-isobutyl-5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]phenyl}acetamide

N-(4-formylphenyl)acetamide (0.041 g) was added to a solution of 1-naphthaldehyde (3-isobutyl-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)hydrazone (0.07 g) in dimethylformamide (1.5 ml). The solution was heated at 165°C for 5 hours. Reaction cooled
10 to room temperature and purified on preparative HPLC to give the title compound (0.051 g).
Mass: 495.79 (M+H)

Example 2

15 7-isobutyl-5-methyl-3-(3-methylthien-2-yl)-2-(1-naphthylmethyl)-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione



20

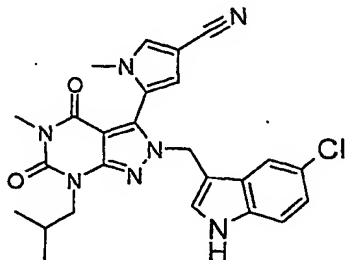
3-methyl-2-thiophenecarbaldehyde (0.063 g) and triethylamine (0.1 ml) was added to a solution of 1-naphthaldehyde (3-isobutyl-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)hydrazone (0.0875 g) in dimethylformamide (1.5 ml). The solution was heated at 90°C for 24 hours. Reaction cooled to room temperature and purified on preparative HPLC to give the
25 title compound (0.072 g). Mass: 458.87 (M+H).

- 22 -

Example 3

5-{2-[(5-chloro-1*H*-indol-3-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-1-methyl-1*H*-pyrrole-3-carbonitrile

5



(a) **5-chloro-1*H*-indole-3-carbaldehyde (3-isobutyl-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)hydrazone**

10 6-Hydrazino-1-isobutyl-3-methylpyrimidine-2,4(1*H*,3*H*)-dione was reacted with 5-chloro-1*H*-indole-3-carbaldehyde as described in example 1 to give the subtitle compound.

(b) **5-{2-[(5-chloro-1*H*-indol-3-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-1-methyl-1*H*-pyrrole-3-carbonitrile**

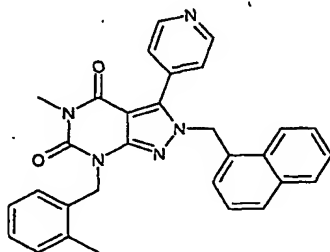
15 5-formyl-1-methyl-1*H*-pyrrole-3-carbonitrile (0.032 g) and piperidine (0.05 ml) was added to a solution of 5-chloro-1*H*-indole-3-carbaldehyde (3-isobutyl-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)hydrazone (0.075 g) in dimethylformamide (1.5 ml). The solution was heated at 50°C for 5 hours. Reaction cooled to room temperature and purified on preparative HPLC to give the title compound (0.058 g). Mass: 490.16 (M+H).

20

Example 4

5-methyl-7-(2-methylbenzyl)-2-(1-naphthylmethyl)-3-pyridin-4-yl-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione

5



10 **(a) 6-hydrazino-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione**

Hydrazine hydrate (12.7 ml) was added to a suspension 6-chloro-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione (10 g) in ethanol (190 ml). The mixture was heated at 75°C for 40 hours, cooled to room temperature. The yellow solid precipitated was filtered and dried give the subtitle compound (8.5 g). Mass: 156.76 (M+H).

15

(b) 1-naphthaldehyde (1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)hydrazone
6-hydrazino-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione (11.5 g) was dissolved in warm methanol (690 ml) and treated with 1-naphthaldehyde (11.88 g). After 2 hours, the precipitated light yellow solid was filtered and dried to give the subtitle compound (15 g). Mass: 294.90

20 (M+H).

(c) 5-methyl-2-(1-naphthylmethyl)-3-pyridin-4-yl-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione

Isonicotinaldehyde (0.87 g) was added to a solution of 1-naphthaldehyde (1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)hydrazone (2.0 g) in dimethylformamide (66 ml) and isopropanol (16 ml). Piperidine (0.66 ml) was added followed by glacial acetic acid (0.08 ml). The solution was heated at 120°C for 16 hours. Reaction cooled to room temperature,

25

- 24 -

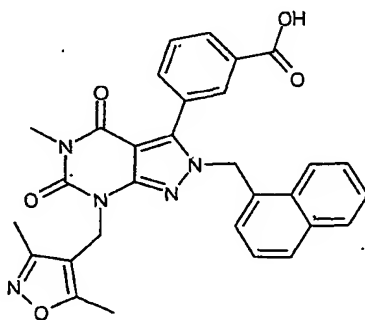
solids precipitated was filtered, and dried to give the subtitle compound (1.63 g). Mass: 383.93 (M+H).

5 (d) 5-methyl-7-(2-methylbenzyl)-2-(1-naphthylmethyl)-3-pyridin-4-yl-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione

1-(chloromethyl)-2-methylbenzene (0.045 ml) and potassium carbonate (0.6 g) were added to a solution of 5-methyl-2-(1-naphthylmethyl)-3-pyridin-4-yl-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (2 ml). The mixture was heated at 80°C for 18 hours then cooled to room temperature. Solids removed by filtration and the crude product was purified on preparative
10 HPLC to give the title compound (0.057 g). Mass: 487.87 (M+H).

Example 5

15 3-[7-[(3,5-dimethylisoxazol-4-yl)methyl]-5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]benzoic acid



(a) Resin bound 3-formylbenzoic acid

20 Diisopropylcarbodiimide (0.378 ml) followed by 4-dimethylaminopyridine (0.02 g) was added to a suspension of Wang resin (0.5 g; 1.2 mmol/g) in dimethylformamide (4 ml), and the mixture was shaken at room temperature for 4 hours. The resin was filtered and washed (3 times) DMF, CH₂Cl₂, MeOH, CH₂Cl₂, and dried in vacuum to give the subtitle compound.

- 25 -

(b) Resin bound 3-[5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-*d*]pyrimidin-3-yl]benzoic acid

1-naphthaldehyde (1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)hydrazone (2.12 g) and triethylamine (0.8 ml) was added to a suspension of Resin bound 3-formylbenzoic acid in dimethylformamide (15 ml), and the mixture was shaken at 90°C for 16 hours. The resin was filtered and washed (3 times) DMF, CH₂Cl₂, MeOH, CH₂Cl₂, and dried in vacuum to give the subtitle compound.

(c) Resin bound 3-[7-[(3,5-dimethylisoxazol-4-yl)methyl]-5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-*d*]pyrimidin-3-yl]benzoic acid

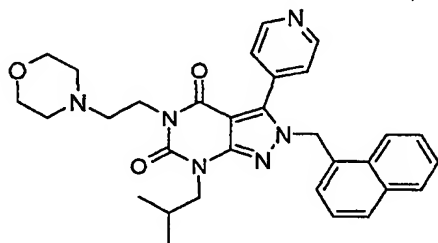
4-(chloromethyl)-3,5-dimethylisoxazole (0.145 g) was added to a suspension of Resin bound 3-[5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-*d*]pyrimidin-3-yl]benzoic acid (0.120 g) and potassium carbonate (0.397 g) in dimethylformamide (1 ml). Reaction mixture was shaken at 85°C for 20 hours. The resin was filtered and washed (3 times) DMF, H₂O, DMF, CH₂Cl₂, MeOH, CH₂Cl₂, and dried in vacuum to give the subtitle compound.

(d) 3-[7-[(3,5-dimethylisoxazol-4-yl)methyl]-5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-*d*]pyrimidin-3-yl]benzoic acid

Resin bound 3-[7-[(3,5-dimethyl-4-isoxazolyl)methyl]-5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-*d*]pyrimidin-3-yl]benzoic acid (0.12g) was treated with 15% TFA in dichloromethane (1 ml) for 2 hours. The resin was filtered and washed (2 times) with dichloromethane. Combined filtrates were concentrated, and crude product was purified on preparative HPLC to give the title compound (0.013 g). Mass: 535.86 (M+H).

Example 6**7-Isobutyl-5-(2-morpholin-4-ylethyl)-2-(1-naphthylmethyl)-3-pyridin-4-yl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione**

5

**(a) 6-hydrazino-1-isobutylpyrimidine-2,4(1H,3H)-dione**

10 Hydrazine hydrate (5.9 ml) was added to a solution of 6-chloro-1-isobutylpyrimidine-2,4(1H,3H)-dione synthesized according to procedure described in *Heterocycles*, 1990, 31(9), 1641-1646, (5.9 g) in ethanol (100 ml). The mixture was heated at reflux for 16 hours, cooled to room temperature and then evaporated under reduced pressure. The residue was crystallized from ethanol to give the subtitle compound (5.8 g).

15

(b) 1-naphthaldehyde (3-isobutyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)hydrazone
6-hydrazino-1-isobutylpyrimidine-2,4(1H,3H)-dione (1.8 g) was dissolved in warm methanol (90 ml) and treated with 1-naphthaldehyde (1.5 g). After 24 hours, the precipitated solid was filtered and dried to give the subtitle compound (3.03 g).

20

(c) 7-isobutyl-2-(1-naphthylmethyl)-3-pyridin-4-yl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione

1-naphthaldehyde (3-isobutyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)hydrazone (3.4 g) was dissolved in a solution of dimethylformamide (99 ml) and isopropanol (24 ml).
25 isonicotinaldehyde (1.3 g) was added followed by piperidine (0.99 ml) and acetic acid (0.12 ml). The mixture was stirred at room temperature for 18 hours. Solvents were removed under reduced pressure. Crude residue was crystallized in methanol/water to give the title compound (3.28 g). Mass: 425.95 (M+H).

- 27 -

(d) 7-Isobutyl-5-(2-morpholin-4-ylethyl)-2-(1-naphthylmethyl)-3-pyridin-4-yl-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione

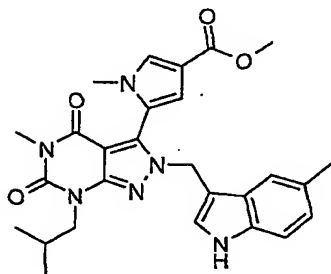
4-(2-chloroethyl)morpholine hydrochloride (0.0435 g) followed by DBU (0.094 g) were
5 added to a solution of 7-isobutyl-2-(1-naphthylmethyl)-3-pyridin-4-yl-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (0.0668 g) in dimethylformamide (1 ml). The mixture was heated at 80°C for 18 hours then cooled to room temperature. The crude reaction was purified on preparative HPLC to give the title compound (0.077 g). Mass: 538.90 (M+H).

10

Example 7

methyl 5-{7-isobutyl-5-methyl-2-[(5-methyl-1*H*-indol-3-yl)methyl]-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-1-methyl-1*H*-pyrrole-3-carboxylate

15



This compound was made following the procedure described above, starting with 6-hydrazino-1-isobutyl-3-methylpyrimidine-2,4(1*H*,3*H*)-dione, and condensing first with 5-methyl-1*H*-indole-3-carbaldehyde, followed by methyl 5-formyl-1-methyl-1*H*-pyrrole-3-carboxylate. Mass: 503.20 (M+H).

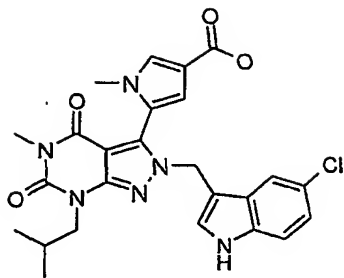
20

Example 8

5-{2-[(5-chloro-1*H*-indol-3-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-1-methyl-1*H*-pyrrole-3-carboxylic acid

25

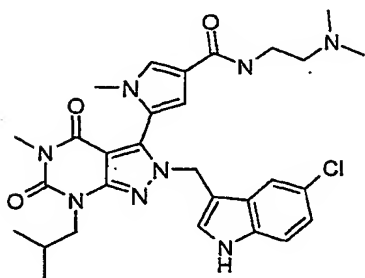
- 28 -



This compound was made following the procedure described above, starting with 6-hydrazino-1-isobutyl-3-methylpyrimidine-2,4(1*H*,3*H*)-dione, and condensing first with 5-chloro-1*H*-indole-3-carbaldehyde, followed by 5-formyl-1-methyl-1*H*-pyrrole-3-carboxylic acid. Mass: 509.18 (M+H).

Example 9

5-{2-[(5-chloro-1*H*-indol-3-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-*N*-[2-(dimethylamino)ethyl]-1-methyl-1*H*-pyrrole-3-carboxamide



15

Diethyl cyanophosphonate (0.0466 g) followed by triethylamine (0.160 ml) were added to a solution of 5-{2-[(5-chloro-1*H*-indol-3-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-1-methyl-1*H*-pyrrole-3-carboxylic acid (0.072 g) and *N,N*-dimethylethane-1,2-diamine (0.049 g) in dimethylformamide (2 ml) at 0°C. The mixture was stirred at ice-cold temperature for 1 hour then at room temperature for 3 hours.

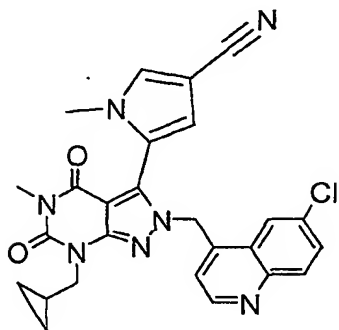
20

The crude reaction was purified on preparative HPLC to give the title compound (0.048 g).
Mass: 579.25 (M+H).

Example 10

5

5-[2-[(6-chloro-4-quinolinyl)methyl]-7-(cyclopropylmethyl)-4,5,6,7-tetrahydro-5-methyl-4,6-dioxo-2H-pyrazolo[3,4-d]pyrimidin-3-yl]-1-methyl-1H-pyrrole-3-carbonitrile



10

This compound was made following the procedure described above, starting with 1-(cyclopropylmethyl)-6-hydrazino-3-methylpyrimidine-2,4(1*H*,3*H*)-dione synthesized according

to the procedure used in example 1 for the corresponding isobutyl substituted compound, and condensing first with 6-chloroquinoline-4-carbaldehyde, followed by 5-formyl-1-methyl-1*H*-pyrrole-3-carbonitrile. Mass: 500.11 (M+H).

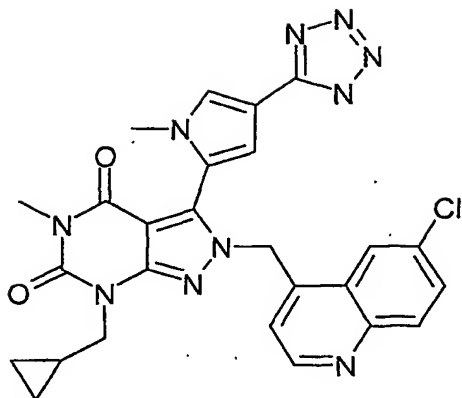
20

Example 11

2-[(6-chloroquinolin-4-yl)methyl]-7-(cyclopropylmethyl)-5-methyl-3-[1-methyl-4-(1*H*-tetrazol-5-yl)-1*H*-pyrrol-2-yl]-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione

25

- 30 -

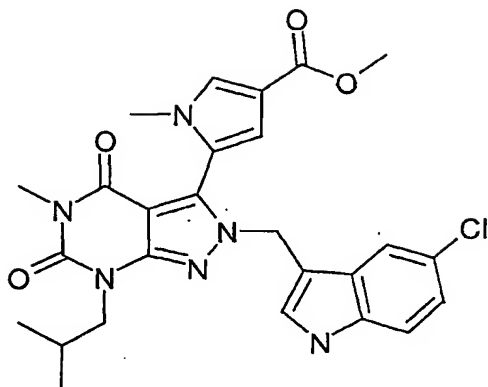


- 5 Sodium azide (0.054 g) and ammonium chloride (0.044 g) were added to a solution of 5-[2-
 [(6-chloro-4-quinoliny)methyl]-7-(cyclopropylmethyl)-4,5,6,7-tetrahydro-5-methyl-4,6-
 dioxo-2H-pyrazolo[3,4-d]pyrimidin-3-yl]-1-methyl-1H-pyrrole-3-carbonitrile (0.083 g) in
 dimethylformamide (5 ml) at 0°C. The mixture was heated at 120°C for 31 hour. The crude
 reaction was purified on preparative HPLC to give the title compound (0.058 g). Mass: 543.08
 10 (M+H).

Example 12

- 15 methyl 5-{2-[(5-chloro-1H-indol-3-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-
 tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl}-1-methyl-1H-pyrrole-3-carboxylate

- 31 -

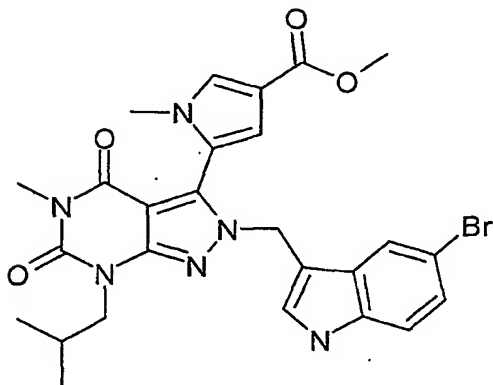


This compound was made following the procedure described above, starting with 6-
 5 hydrazino-1-isobutyl-3-methylpyrimidine-2,4(1*H*,3*H*)-dione, and condensing first with 5-
 chloro-1*H*-indole-3-carbaldehyde, followed by methyl 5-formyl-1-methyl-1*H*-pyrrole-3-
 carboxylate. Mass: 523.15 (M+H).

10 Example 13

**methyl 5-{2-[(5-bromo-1*H*-indol-3-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-
 tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-1-methyl-1*H*-pyrrole-3-carboxylate**

15



- 32 -

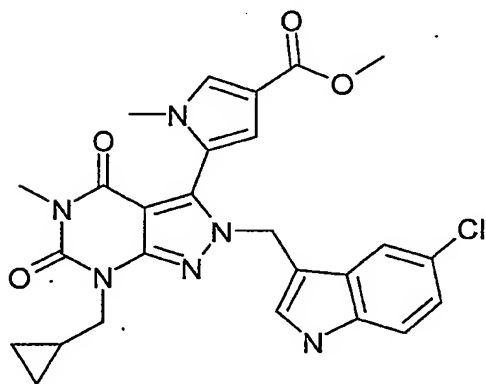
This compound was made following the procedure described above, starting with 6-hydrazino-1-isobutyl-3-methylpyrimidine-2,4(1*H*,3*H*)-dione, and condensing first with 5-bromo-1*H*-indole-3-carbaldehyde, followed by methyl 5-formyl-1-methyl-1*H*-pyrrole-3-carboxylate.

5

Example 14

methyl 5-[2-[(5-chloro-1*H*-indol-3-yl)methyl]-7-(cyclopropylmethyl)-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-1-methyl-1*H*-pyrrole-3-carboxylate

10



15

This compound was made following the procedure described above, starting with 1-(cyclopropylmethyl)-6-hydrazino-3-methylpyrimidine-2,4(1*H*,3*H*)-dione, and condensing first with 5-chloro-1*H*-indole-3-carbaldehyde, followed by methyl 5-formyl-1-methyl-1*H*-pyrrole-3-carboxylate. Mass: 520.97 (M+H).

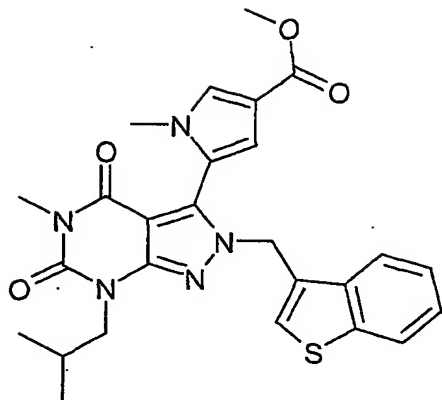
20

Example 15

methyl 5-[2-(1-benzothien-3-ylmethyl)-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-1-methyl-1*H*-pyrrole-3-carboxylate

25

- 33 -

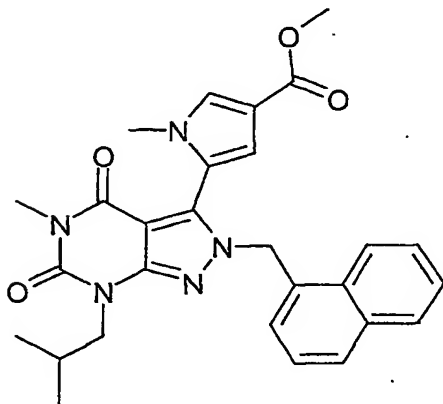


This compound was made following the procedure described above, starting with 6-hydrazino-1-isobutyl-3-methylpyrimidine-2,4(1*H*,3*H*)-dione, and condensing first with 1-benzothiophene-3-carbaldehyde, followed by methyl 5-formyl-1-methyl-1*H*-pyrrole-3-carboxylate. Mass: 506.31 (M+H).

Example 16

10

methyl 5-[7-isobutyl-5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-1-methyl-1*H*-pyrrole-3-carboxylate



15

This compound was made following the procedure described above, starting with 6-hydrazino-1-isobutyl-3-methylpyrimidine-2,4(1*H*,3*H*)-dione, and condensing first with 1-

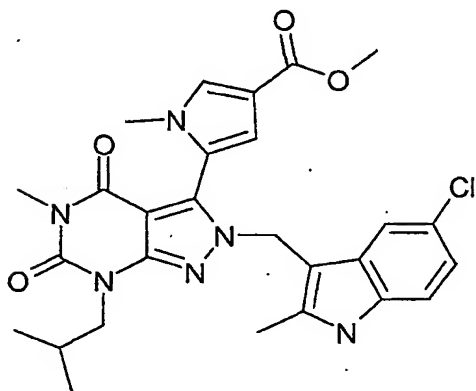
- 34 -

naphthaldehyde, followed by methyl 5-formyl-1-methyl-1*H*-pyrrole-3-carboxylate. Mass: 500.38 (M+H).

Example 17

5

methyl 5-{2-[(5-chloro-2-methyl-1*H*-indol-3-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-1-methyl-1*H*-pyrrole-3-carboxylate



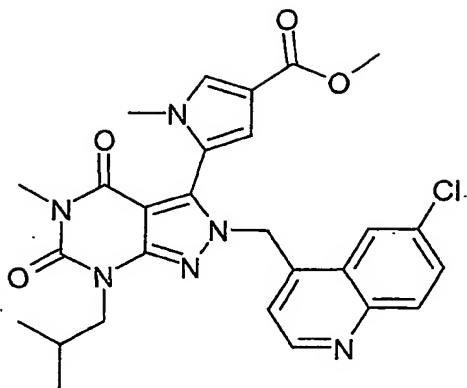
10

This compound was made following the procedure described above, starting with 6-hydrazino-1-isobutyl-3-methylpyrimidine-2,4(1*H*,3*H*)-dione, and condensing first with 5-chloro-2-methyl-1*H*-indole-3-carbaldehyde, followed by methyl 5-formyl-1-methyl-1*H*-pyrrole-3-carboxylate. Mass: 537.01 (M+H).

Example 18

20 methyl 5-{2-[(6-chloroquinolin-4-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-1-methyl-1*H*-pyrrole-3-carboxylate

- 35 -

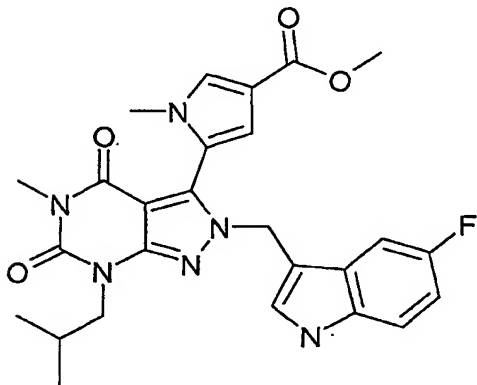


This compound was made following the procedure described above, starting with 6-
 5 hydrazino-1-isobutyl-3-methylpyrimidine-2,4(1*H*,3*H*)-dione, and condensing first with 6-
 chloroquinoline-4-carbaldehyde, followed by methyl 5-formyl-1-methyl-1*H*-pyrrole-3-
 carboxylate. Mass: 535.05 (M+H).

Example 19

10

methyl 5-{2-[(5-fluoro-1*H*-indol-3-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-
 tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-1-methyl-1*H*-pyrrole-3-carboxylate



15

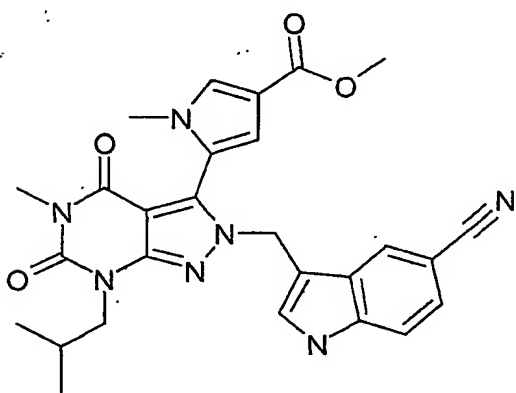
This compound was made following the procedure described above, starting with 6-
 hydrazino-1-isobutyl-3-methylpyrimidine-2,4(1*H*,3*H*)-dione, and condensing first with 5-

- 36 -

fluoro-1*H*-indole-3-carbaldehyde, followed by methyl 5-formyl-1-methyl-1*H*-pyrrole-3-carboxylate. Mass: 507.05 (M+H).

Example 20

methyl 5-{2-[(5-cyano-1*H*-indol-3-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-1-methyl-1*H*-pyrrole-3-carboxylate

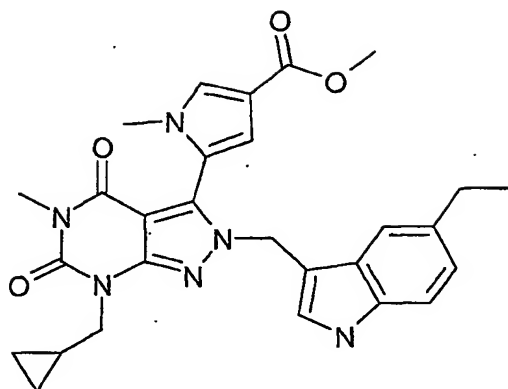


This compound was made following the procedure described above, starting with 6-hydrazino-1-isobutyl-3-methylpyrimidine-2,4(1*H*,3*H*)-dione, and condensing first with 3-formyl-1*H*-indole-5-carbonitrile, followed by methyl 5-formyl-1-methyl-1*H*-pyrrole-3-carboxylate. Mass: 514.05 (M+H).

Example 21

methyl 5-{7-(cyclopropylmethyl)-2-[(5-ethyl-1*H*-indol-3-yl)methyl]-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-1-methyl-1*H*-pyrrole-3-carboxylate

- 37 -

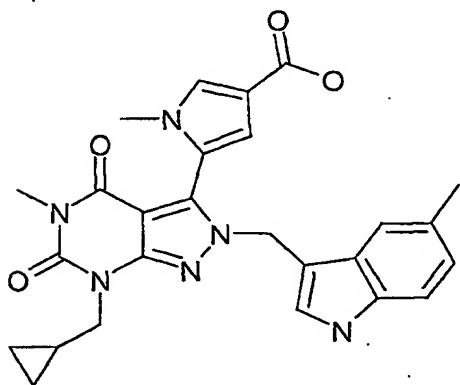


This compound was made following the procedure described above, starting with 1-
 5 (cyclopropylmethyl)-6-hydrazino-3-methylpyrimidine-2,4(1*H*,3*H*)-dione, and condensing
 first with 5-ethyl-1*H*-indole-3-carbaldehyde, followed by methyl 5-formyl-1-methyl-1*H*-
 pyrrole-3-carboxylate. Mass: 515.25 (M+H).

Example 22

10

5-{7-(cyclopropylmethyl)-5-methyl-2-[(5-methyl-1*H*-indol-3-yl)methyl]-4,6-dioxo-4,5,6,7-
 tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-1-methyl-1*H*-pyrrole-3-carboxylic acid



15

This compound was made following the procedure described above, starting with 1-
 (cyclopropylmethyl)-6-hydrazino-3-methylpyrimidine-2,4(1*H*,3*H*)-dione, and condensing

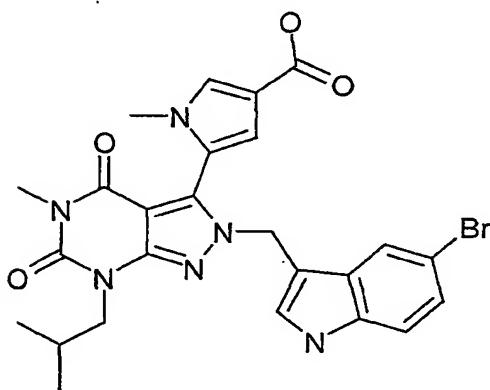
- 38 -

first with 5-methyl-1*H*-indole-3-carbaldehyde, followed by 5-formyl-1-methyl-1*H*-pyrrole-3-carboxylic acid. Mass: 487.23 (M+H).

Example 23

5

5-{2-[(5-bromo-1*H*-indol-3-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-1-methyl-1*H*-pyrrole-3-carboxylic acid



10

This compound was made following the procedure described above, starting with 6-hydrazino-1-isobutyl-3-methylpyrimidine-2,4(1*H*,3*H*)-dione, and condensing first with 5-bromo-1*H*-indole-3-carbaldehyde, followed by 5-formyl-1-methyl-1*H*-pyrrole-3-carboxylic acid.

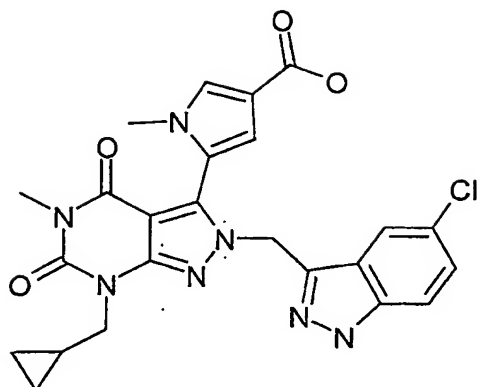
15

Example 24

5-[2-[(5-chloro-1*H*-indazol-3-yl)methyl]-7-(cyclopropylmethyl)-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-1-methyl-1*H*-pyrrole-3-carboxylic acid

20

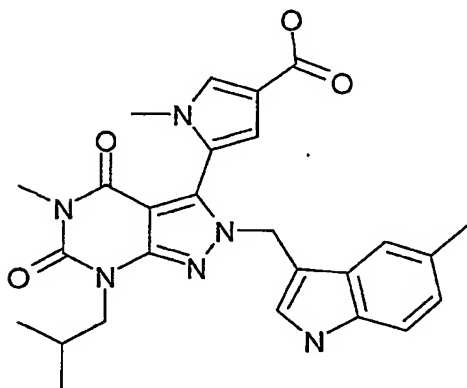
- 39 -



This compound was made following the procedure described above, starting with 1-
 5 (cyclopropylmethyl)-6-hydrazino-3-methylpyrimidine-2,4(1*H*,3*H*)-dione, and condensing
 first with 5-chloro-1*H*-indazole-3-carbaldehyde, followed by 5-formyl-1-methyl-1*H*-pyrrole-
 3-carboxylic acid. Mass: 508.13 (M+H).

10 Example 25

5-{7-isobutyl-5-methyl-2-[(5-methyl-1*H*-indol-3-yl)methyl]-4,6-dioxo-4,5,6,7-tetrahydro-
 2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-1-methyl-1*H*-pyrrole-3-carboxylic acid



15

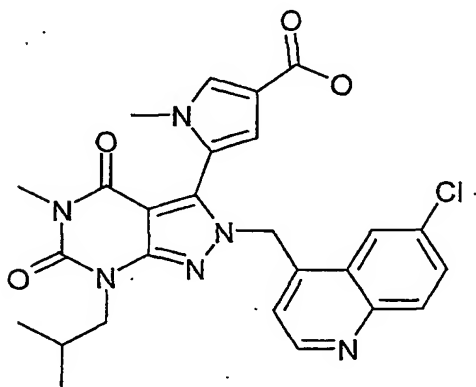
- 40 -

This compound was made following the procedure described above, starting with 6-hydrazino-1-isobutyl-3-methylpyrimidine-2,4(1*H*,3*H*)-dione, and condensing first with 5-methyl-1*H*-indole-3-carbaldehyde, followed by 5-formyl-1-methyl-1*H*-pyrrole-3-carboxylic acid. Mass: 489.16 (M+H).

5

Example 26

5-{2-[(6-chloroquinolin-4-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-
10 2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-1-methyl-1*H*-pyrrole-3-carboxylic acid



15 This compound was made following the procedure described above, starting with 6-hydrazino-1-isobutyl-3-methylpyrimidine-2,4(1*H*,3*H*)-dione, and condensing first with 6-chloroquinoline-4-carbaldehyde, followed by 5-formyl-1-methyl-1*H*-pyrrole-3-carboxylic acid. Mass: 521.09 (M+H).

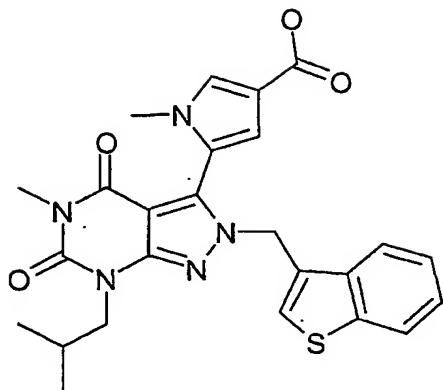
20

Example 27

5-[2-(1-benzothien-3-ylmethyl)-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-
pyrazolo[3,4-*d*]pyrimidin-3-yl]-1-methyl-1*H*-pyrrole-3-carboxylic acid

25

- 41 -

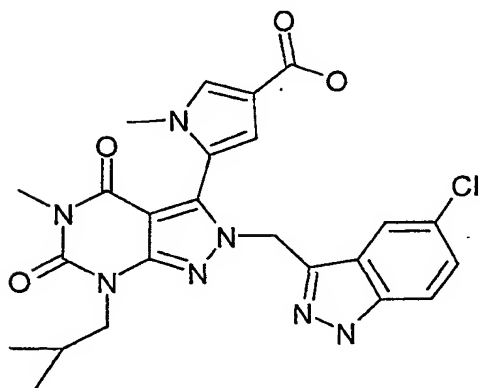


This compound was made following the procedure described above, starting with 6-hydrazino-1-isobutyl-3-methylpyrimidine-2,4(1*H*,3*H*)-dione, and condensing first with 1-
 5 benzothiophene-3-carbaldehyde, followed by 5-formyl-1-methyl-1*H*-pyrrole-3-carboxylic acid. Mass: 492.09 (M+H).

Example 28

10

5-{2-[(5-chloro-1*H*-indazol-3-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-1-methyl-1*H*-pyrrole-3-carboxylic acid



15

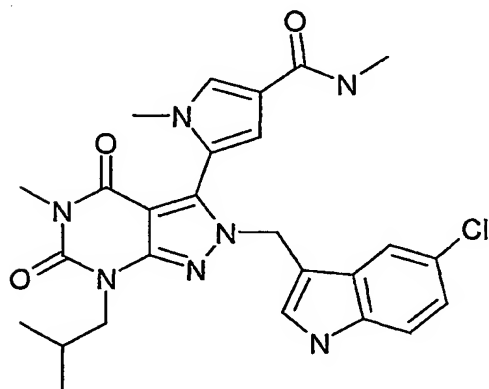
This compound was made following the procedure described above, starting with 6-hydrazino-1-isobutyl-3-methylpyrimidine-2,4(1*H*,3*H*)-dione, and condensing first with 5-

- 42 -

chloro-1*H*-indazole-3-carbaldehyde, followed by 5-formyl-1-methyl-1*H*-pyrrole-3-carboxylic acid. Mass: 510.13 (M+H).

5 Example 29

5-{2-[(5-chloro-1*H*-indol-3-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-*N*,1-dimethyl-1*H*-pyrrole-3-carboxamide



This compound was synthesized by the reaction of 5-{2-[(5-chloro-1*H*-indol-3-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-1-methyl-1*H*-pyrrole-3-carboxylic acid and methylamine using diethyl cyanophosphonate as a coupling reagent. Mass: 522.19 (M+H).

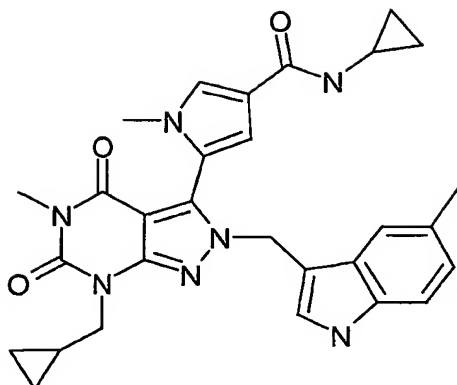
15

Example 30

N-cyclopropyl-5-{7-(cyclopropylmethyl)-5-methyl-2-[(5-methyl-1*H*-indol-3-yl)methyl]-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-1-methyl-1*H*-pyrrole-3-carboxamide

20

- 43 -

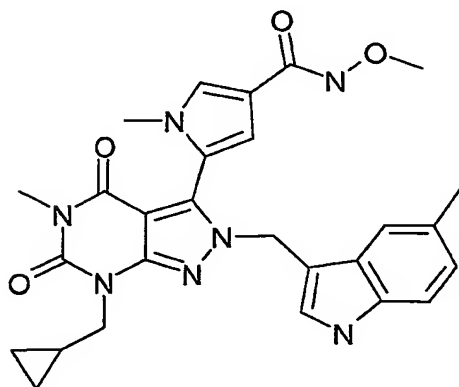


This compound was synthesized by the reaction of 5-{7-(cyclopropylmethyl)-5-methyl-2-[(5-methyl-1H-indol-3-yl)methyl]-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl}-1-methyl-1H-pyrrole-3-carboxylic acid and cyclopropylamine using diethyl cyanophosphonate as a coupling reagent. Mass: 526.22 (M+H).

10 Example 31

5-{7-(cyclopropylmethyl)-5-methyl-2-[(5-methyl-1H-indol-3-yl)methyl]-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl}-N-methoxy-1-methyl-1H-pyrrole-3-carboxamide

15



- 44 -

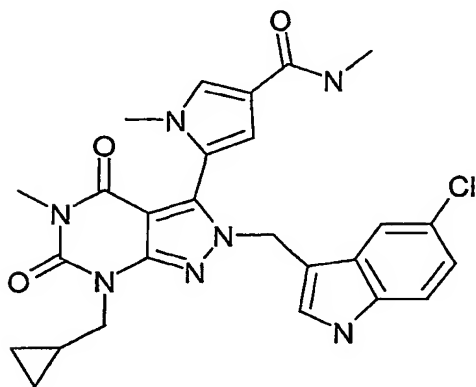
This compound was synthesized by the reaction of 5-{7-(cyclopropylmethyl)-5-methyl-2-[(5-methyl-1*H*-indol-3-yl)methyl]-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-1-methyl-1*H*-pyrrole-3-carboxylic acid and methoxylamine hydrochloride using diethyl cyanophosphonate as a coupling reagent. Mass: 516.21 (M+H).

5

Example 32

5-[2-[(5-chloro-1*H*-indol-3-yl)methyl]-7-(cyclopropylmethyl)-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-*N*,1-dimethyl-1*H*-pyrrole-3-carboxamide

10



This compound was synthesized by the reaction of 5-[2-[(5-chloro-1*H*-indol-3-yl)methyl]-7-(cyclopropylmethyl)-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-1-methyl-1*H*-pyrrole-3-carboxylic acid and methlamine using diethyl cyanophosphonate as a coupling reagent. Mass: 520.15 (M+H).

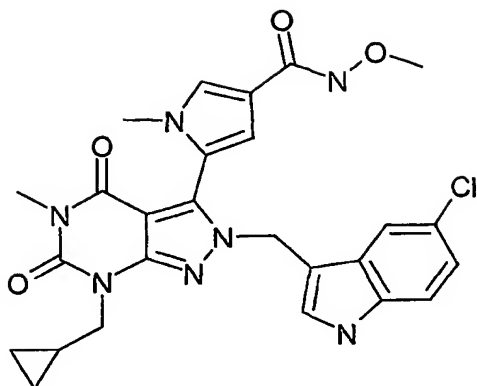
15

Example 33

20

5-[2-[(5-chloro-1*H*-indol-3-yl)methyl]-7-(cyclopropylmethyl)-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-*N*-methoxy-1-methyl-1*H*-pyrrole-3-carboxamide

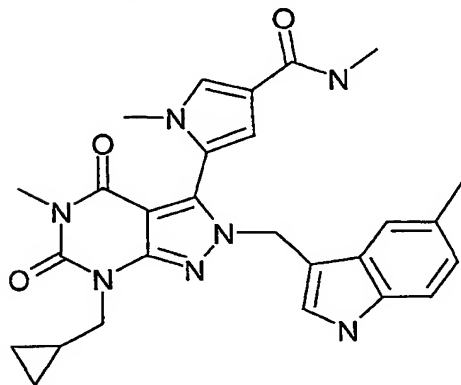
- 45 -



This compound was synthesized by the reaction of 5-[2-[(5-chloro-1*H*-indol-3-yl)methyl]-7-(cyclopropylmethyl)-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-1-methyl-1*H*-pyrrole-3-carboxylic acid and methoxylamine hydrochloride using diethyl cyanophosphonate as a coupling reagent. Mass: 536.18 (M+H).

Example 34

- 10 5-{7-(cyclopropylmethyl)-5-methyl-2-[(5-methyl-1*H*-indol-3-yl)methyl]-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-N,1-dimethyl-1*H*-pyrrole-3-carboxamide

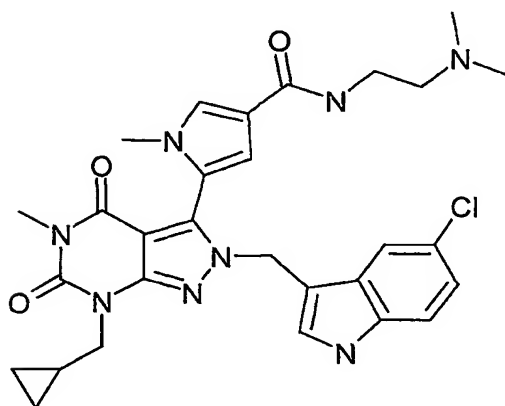


- 15 This compound was synthesized by the reaction of 5-{7-(cyclopropylmethyl)-5-methyl-2-[(5-methyl-1*H*-indol-3-yl)methyl]-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-1-methyl-1*H*-pyrrole-3-carboxylic acid and methylamine using diethyl cyanophosphonate as a coupling reagent. Mass: 500.25 (M+H).

- 46 -

Example 35

5-[2-[(5-chloro-1*H*-indol-3-yl)methyl]-7-(cyclopropylmethyl)-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-*N*-[2-(dimethylamino)ethyl]-1-methyl-1*H*-pyrrole-3-carboxamide



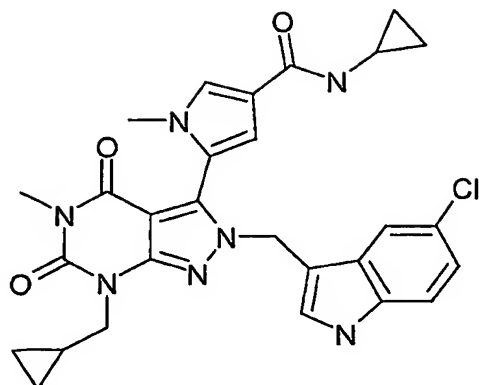
This compound was synthesized by the reaction of 5-[2-[(5-chloro-1*H*-indol-3-yl)methyl]-7-(cyclopropylmethyl)-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-1-methyl-1*H*-pyrrole-3-carboxylic acid and *N,N*-dimethylethane-1,2-diamine using diethyl cyanophosphonate as a coupling reagent. Mass: 577.31 (M+H).

Example 36

15

5-[2-[(5-chloro-1*H*-indol-3-yl)methyl]-7-(cyclopropylmethyl)-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-*N*-cyclopropyl-1-methyl-1*H*-pyrrole-3-carboxamide

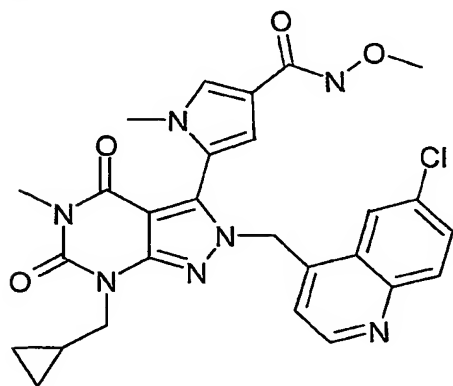
- 47 -



This compound was synthesized by the reaction of 5-[2-[(5-chloro-1*H*-indol-3-yl)methyl]-7-(cyclopropylmethyl)-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-1-methyl-1*H*-pyrrole-3-carboxylic acid and cyclopropylamine using diethyl
 5 cyanophosphonate as a coupling reagent. Mass: 546.19 (M+H).

Example 37

10 **5-[2-[(6-chloroquinolin-4-yl)methyl]-7-(cyclopropylmethyl)-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-*N*-methoxy-1-methyl-1*H*-pyrrole-3-carboxamide**



15 This compound was synthesized by the reaction 5-[2-[(6-chloroquinolin-4-yl)methyl]-7-(cyclopropylmethyl)-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-

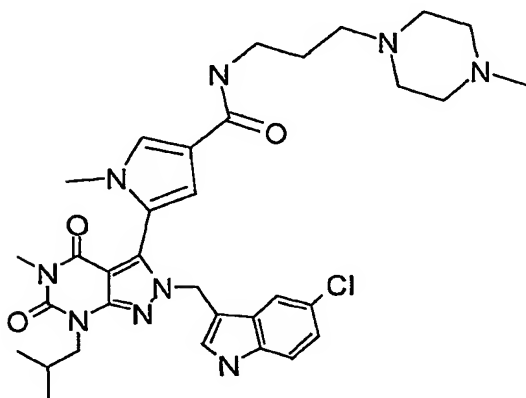
- 48 -

yl]-1-methyl-1*H*-pyrrole-3-carboxylic acid and methoxylamine hydrochloride using diethyl cyanophosphonate as a coupling reagent. Mass: 548.13 (M+H).

Example 38

5

5-{2-[(5-chloro-1*H*-indol-3-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-1-methyl-N-[3-(4-methylpiperazin-1-yl)propyl]-1*H*-pyrrole-3-carboxamide



10

This compound was synthesized by the reaction of 5-{2-[(5-chloro-1*H*-indol-3-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-1-methyl-1*H*-pyrrole-3-carboxylic acid and 3-(4-methylpiperazin-1-yl)propylamine using diethyl cyanophosphonate as a coupling reagent. Mass: 648.20 (M+H).

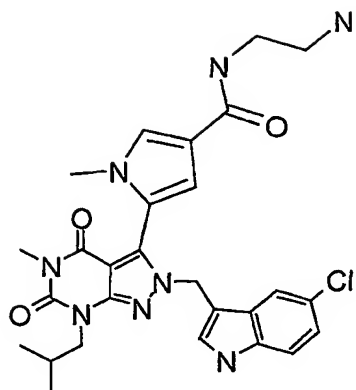
15

Example 39

N-(2-aminoethyl)-5-{2-[(5-chloro-1*H*-indol-3-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-1-methyl-1*H*-pyrrole-3-carboxamide

20

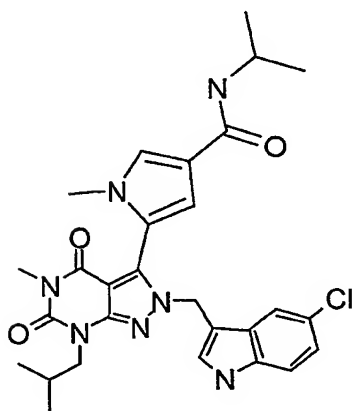
- 49 -



This compound was synthesized by the reaction of 5-{2-[(5-chloro-1*H*-indol-3-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-1-methyl-1*H*-pyrrole-3-carboxylic acid and ethane-1,2-diamine using diethyl cyanophosphonate as a coupling reagent. Mass: 551.15 (M+H).

Example 40

10 5-{2-[(5-chloro-1*H*-indol-3-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-*N*-isopropyl-1-methyl-1*H*-pyrrole-3-carboxamide



15 This compound was synthesized by the reaction of 5-{2-[(5-chloro-1*H*-indol-3-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-1-methyl-

- 50 -

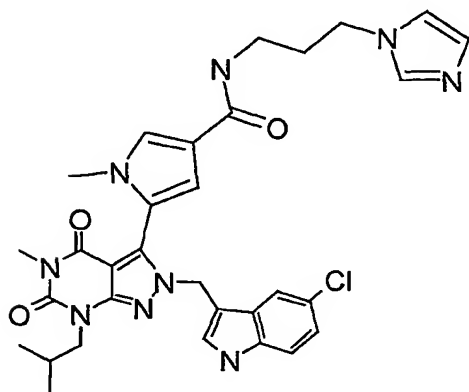
1*H*-pyrrole-3-carboxylic acid and isopropylamine using diethyl cyanophosphonate as a coupling reagent. Mass: 550.14 (M+H).

Example 41

5

5-{2-[(5-chloro-1*H*-indol-3-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-N-[3-(1*H*-imidazol-1-yl)propyl]-1-methyl-1*H*-pyrrole-3-carboxamide

10



15

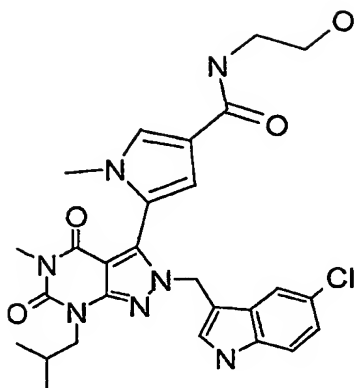
This compound was synthesized by the reaction of 5-{2-[(5-chloro-1*H*-indol-3-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-1-methyl-1*H*-pyrrole-3-carboxylic acid and 3-(1*H*-imidazol-1-yl)propylamine using diethyl cyanophosphonate as a coupling reagent. Mass: 616.15 (M+H).

Example 42

20

5-{2-[(5-chloro-1*H*-indol-3-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-N-(2-hydroxyethyl)-1-methyl-1*H*-pyrrole-3-carboxamide

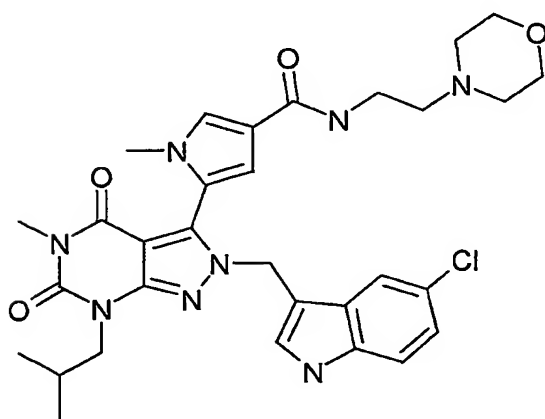
- 51 -



This compound was synthesized by the reaction of 5-{2-[(5-chloro-1*H*-indol-3-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-1-methyl-1*H*-pyrrole-3-carboxylic acid and 2-aminoethanol using diethyl cyanophosphate as a coupling reagent. Mass: 552.16 (M+H).

Example 43

10 5-{2-[(5-chloro-1*H*-indol-3-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-1-methyl-N-(2-morpholin-4-ylethyl)-1*H*-pyrrole-3-carboxamide



15

This compound was synthesized by the reaction of 5-{2-[(5-chloro-1*H*-indol-3-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-1-methyl-

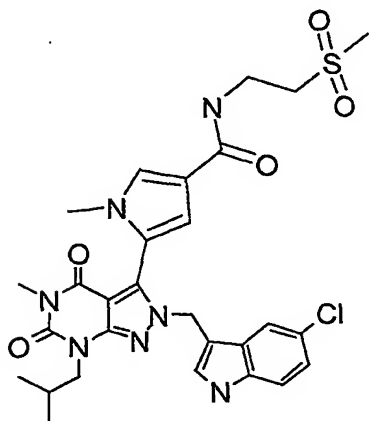
- 52 -

1*H*-pyrrole-3-carboxylic acid and 2-morpholin-4-ylethanamine using diethyl cyanophosphonate as a coupling reagent. Mass: 621.20 (M+H).

Example 44

5

5-{2-[(5-chloro-1*H*-indol-3-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-1-methyl-N-[2-(methylsulfonyl)ethyl]-1*H*-pyrrole-3-carboxamide



10

This compound was synthesized by the reaction of 5-{2-[(5-chloro-1*H*-indol-3-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-1-methyl-1*H*-pyrrole-3-carboxylic acid and 2-(methylsulfonyl)ethylaniline using diethyl

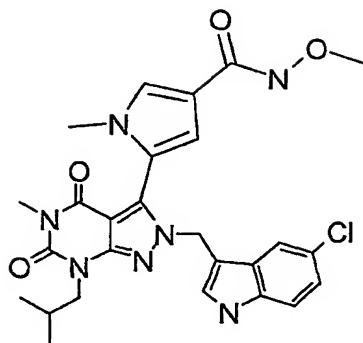
15 cyanophosphonate as a coupling reagent. Mass: 614.00 (M+H).

Example 45

5-{2-[(5-chloro-1*H*-indol-3-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-N-methoxy-1-methyl-1*H*-pyrrole-3-carboxamide

20

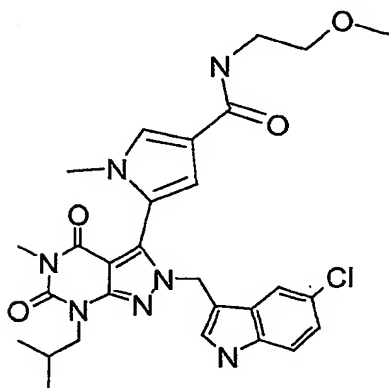
- 53 -



This compound was synthesized by the reaction of 5-{2-[(5-chloro-1*H*-indol-3-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-1-methyl-1*H*-pyrrole-3-carboxylic acid and methoxylamine hydrochloride using diethyl cyanophosphonate as a coupling reagent. Mass: 537.98 (M+H).

Example 46

5- {2-[(5-chloro-1*H*-indol-3-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-*N*-(2-methoxyethyl)-1-methyl-1*H*-pyrrole-3-carboxamide

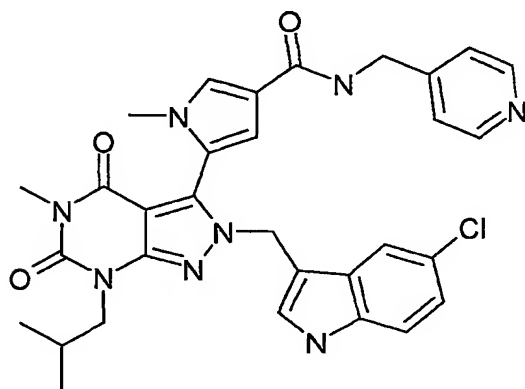


15

This compound was synthesized by the reaction of 5-{2-[(5-chloro-1*H*-indol-3-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-1-methyl-1*H*-pyrrole-3-carboxylic acid and 2-methoxyethylamine using diethyl cyanophosphonate as a coupling reagent. Mass: 566.10 (M+H).

Example 47

5-**{2-[(5-chloro-1H-indol-3-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl}-1-methyl-N-(pyridin-4-ylmethyl)-1H-pyrrole-3-carboxamide**



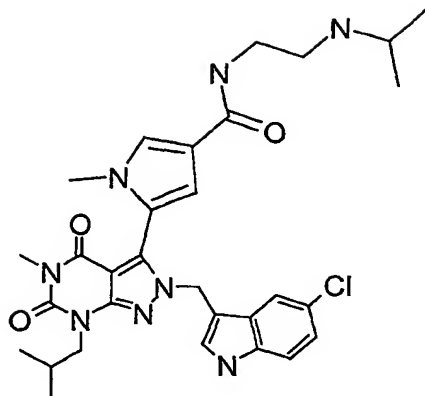
This compound was synthesized by the reaction of 5-**{2-[(5-chloro-1H-indol-3-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl}-1-methyl-1H-pyrrole-3-carboxylic acid** and pyridin-4-ylmethylamine using diethyl cyanophosphonate as a coupling reagent. Mass: 599.15 (M+H).

Example 48

15

5-**{2-[(5-chloro-1H-indol-3-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl}-N-[2-(isopropylamino)ethyl]-1-methyl-1H-pyrrole-3-carboxamide**

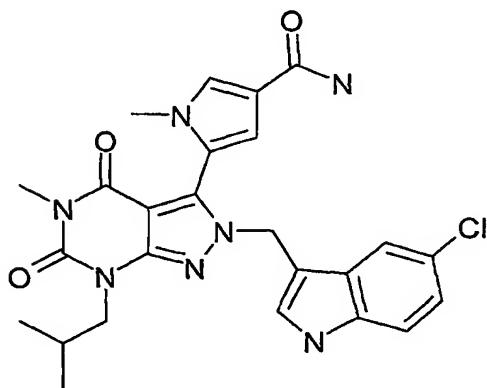
- 55 -



This compound was synthesized by the reaction of 5-{2-[(5-chloro-1*H*-indol-3-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-1-methyl-1*H*-pyrrole-3-carboxylic acid and *N*-isopropylethane-1,2-diamine using diethyl cyanophosphonate as a coupling reagent. Mass: 593.16 (M+H).

Example 49

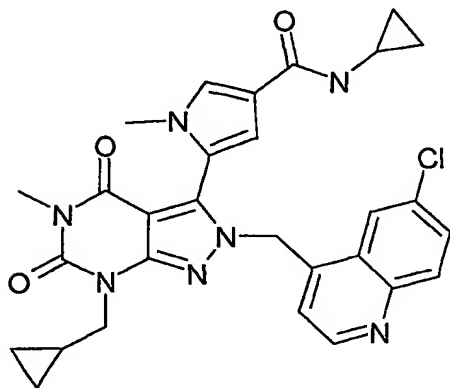
5-{2-[(5-chloro-1*H*-indol-3-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-1-methyl-1*H*-pyrrole-3-carboxamide



This compound was synthesized by the reaction of 5-{2-[(5-chloro-1*H*-indol-3-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-1-methyl-1*H*-pyrrole-3-carboxylic acid and ammonia using diethyl cyanophosphonate as a coupling reagent. Mass: 508.10 (M+H).

Example 50

- 5 **5-[2-[(6-chloroquinolin-4-yl)methyl]-7-(cyclopropylmethyl)-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]-N-cyclopropyl-1-methyl-1H-pyrrole-3-carboxamide**

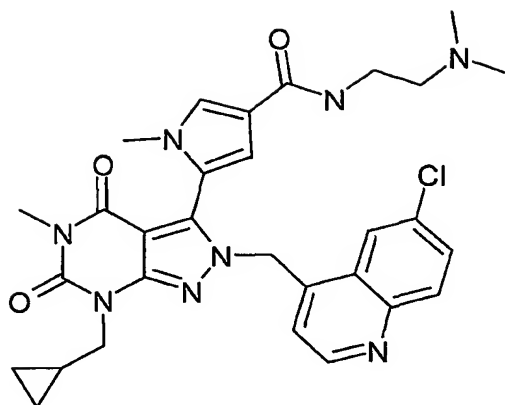


- 10 This compound was synthesized by the reaction of 5-[2-[(6-chloroquinolin-4-yl)methyl]-7-(cyclopropylmethyl)-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]-1-methyl-1H-pyrrole-3-carboxylic acid and cyclopropylamine using diethyl cyanophosphonate as a coupling reagent. Mass: 558.15 (M+H).

15 **Example 51**

5-[2-[(6-chloroquinolin-4-yl)methyl]-7-(cyclopropylmethyl)-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]-N-[2-(dimethylamino)ethyl]-1-methyl-1H-pyrrole-3-carboxamide

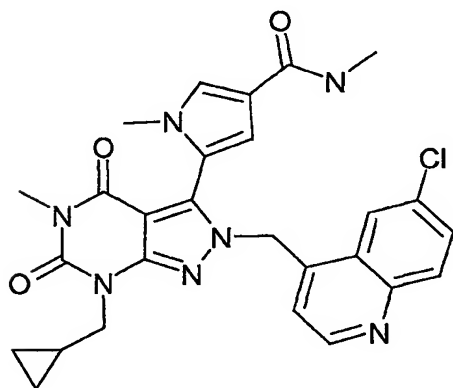
- 57 -



This compound was synthesized by the reaction of 5-[2-[(6-chloroquinolin-4-yl)methyl]-7-(cyclopropylmethyl)-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]-1-methyl-1H-pyrrole-3-carboxylic acid and *N,N*-dimethylethane-1,2-diamine using diethyl cyanophosphonate as a coupling reagent. Mass: 589.35 (M+H).

Example 52

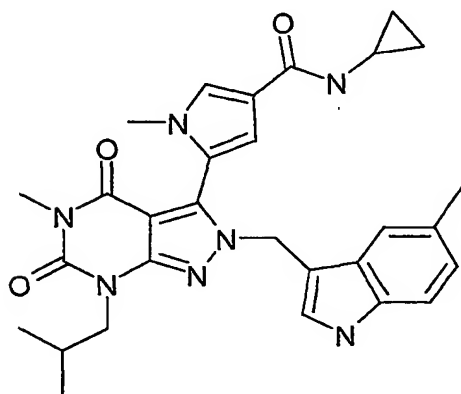
10 5-[2-[(6-chloroquinolin-4-yl)methyl]-7-(cyclopropylmethyl)-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]-N,1-dimethyl-1H-pyrrole-3-carboxamide



This compound was synthesized by the reaction of 5-[2-[(6-chloroquinolin-4-yl)methyl]-7-(cyclopropylmethyl)-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]-1-methyl-1H-pyrrole-3-carboxylic acid and ammonia using diethyl cyanophosphonate as a coupling reagent. Mass: 532.17 (M+H).

Example 53

**N-cyclopropyl-5-{7-isobutyl-5-methyl-2-[(5-methyl-1H-indol-3-yl)methyl]-4,6-dioxo-
5 4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl}-1-methyl-1H-pyrrole-3-
carboxamide**

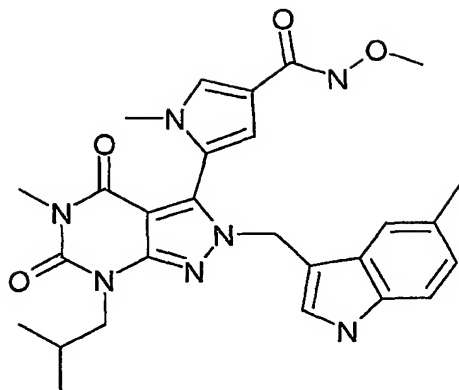


- 10 This compound was synthesized by the reaction of 5-{7-isobutyl-5-methyl-2-[(5-methyl-1H-indol-3-yl)methyl]-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl}-1-methyl-1H-pyrrole-3-carboxylic acid and cyclopropylamine using diethyl cyanophosphonate as a coupling reagent. Mass: 528.30 (M+H).

15 **Example 54**

**5-{7-isobutyl-5-methyl-2-[(5-methyl-1H-indol-3-yl)methyl]-4,6-dioxo-4,5,6,7-tetrahydro-
2H-pyrazolo[3,4-d]pyrimidin-3-yl}-N-methoxy-1-methyl-1H-pyrrole-3-carboxamide**

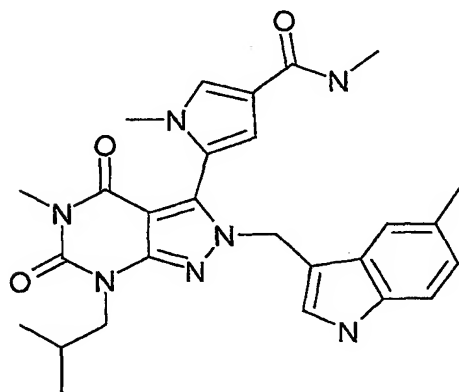
- 59 -



- This compound was synthesized by the reaction of 5-{7-isobutyl-5-methyl-2-[(5-methyl-1*H*-indol-3-yl)methyl]-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-1-methyl-1*H*-pyrrole-3-carboxylic acid and methoxylamine hydrochloride using diethyl cyanophosphonate as a coupling reagent. Mass: 518.28 (M+H).

Example 55

- 10 5-{7-isobutyl-5-methyl-2-[(5-methyl-1*H*-indol-3-yl)methyl]-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-*N*,1-dimethyl-1*H*-pyrrole-3-carboxamide



- 15 This compound was synthesized by the reaction of 5-{7-isobutyl-5-methyl-2-[(5-methyl-1*H*-indol-3-yl)methyl]-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-1-

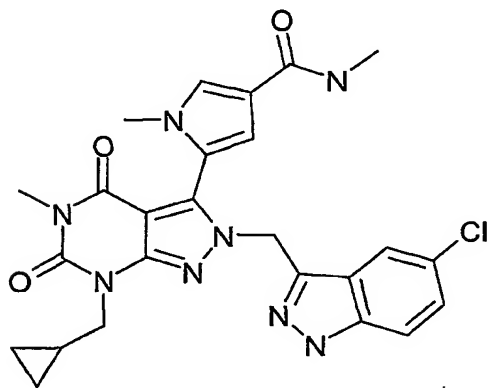
- 60 -

methyl-1*H*-pyrrole-3-carboxylic acid and ammonia using diethyl cyanophosphonate as a coupling reagent. Mass: 502.25 (M+H).

Example 56

5

5-[2-[(5-chloro-1*H*-indazol-3-yl)methyl]-7-(cyclopropylmethyl)-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-N,1-dimethyl-1*H*-pyrrole-3-carboxamide



10

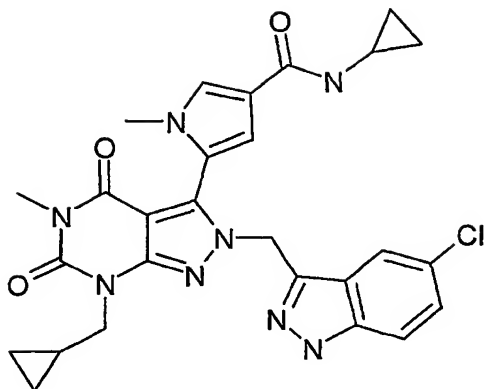
This compound was synthesized by the reaction of 5-[2-[(5-chloro-1*H*-indazol-3-yl)methyl]-7-(cyclopropylmethyl)-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-1-methyl-1*H*-pyrrole-3-carboxylic acid and ammonia using diethyl cyanophosphonate
15 as a coupling reagent. Mass: 521.15 (M+H).

Example 57

5-[2-[(5-chloro-1*H*-indazol-3-yl)methyl]-7-(cyclopropylmethyl)-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-N-cyclopropyl-1-methyl-1*H*-pyrrole-3-carboxamide

20

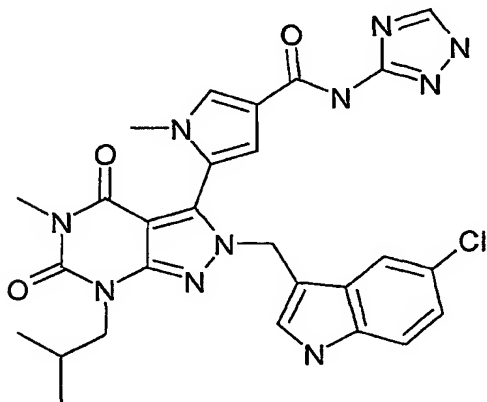
- 61 -



This compound was synthesized by the reaction of 5-[2-[(5-chloro-1*H*-indazol-3-yl)methyl]-7-(cyclopropylmethyl)-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-1-methyl-1*H*-pyrrole-3-carboxylic acid and cyclopropylamine using diethyl cyanophosphonate as a coupling reagent. Mass: 547.19 (M+H).

Example 58

10 **5-{2-[(5-chloro-1*H*-indol-3-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-1-methyl-*N*-1*H*-1,2,4-triazol-3-yl-1*H*-pyrrole-3-carboxamide**



15 This compound was synthesized by the reaction of 5-{2-[(5-chloro-1*H*-indol-3-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-1-methyl-

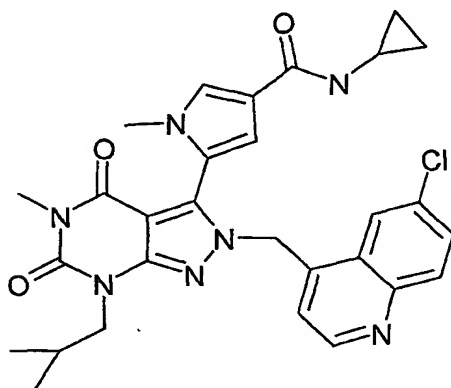
- 62 -

1*H*-pyrrole-3-carboxylic acid and 1*H*-1,2,4-triazol-3-amine using diethyl cyanophosphonate as a coupling reagent. Mass: 575.13 (M+H).

Example 59

5

5-{2-[(6-chloroquinolin-4-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-*N*-cyclopropyl-1-methyl-1*H*-pyrrole-3-carboxamide



10

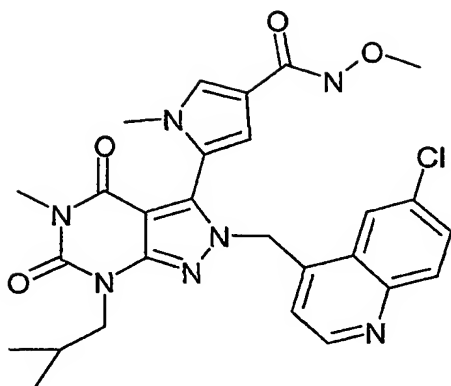
This compound was synthesized by the reaction of 5-{2-[(6-chloroquinolin-4-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-1-methyl-1*H*-pyrrole-3-carboxylic acid and cyclopropylamine using diethyl cyanophosphonate as a coupling reagent. Mass: 560.22 (M+H).

15

Example 60

5-{2-[(6-chloroquinolin-4-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-*N*-methoxy-1-methyl-1*H*-pyrrole-3-carboxamide

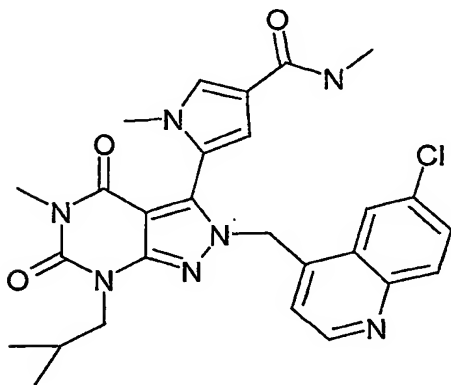
20



This compound was synthesized by the reaction of 5-{2-[(6-chloroquinolin-4-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl}-1-methyl-1H-pyrrole-3-carboxylic acid and methoxylamine hydrochloride using diethyl cyanophosphonate as a coupling reagent. Mass: 550.13 (M+H).

Example 61

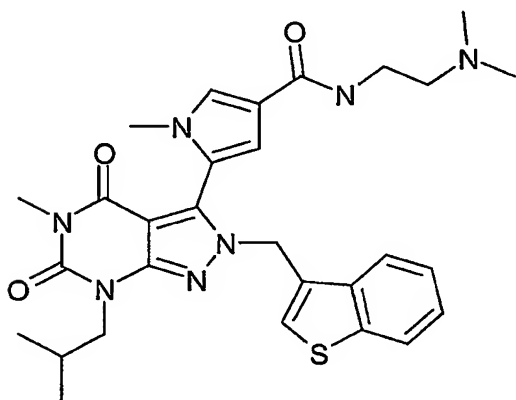
- 10 5-{2-[(6-chloroquinolin-4-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl}-N,1-dimethyl-1H-pyrrole-3-carboxamide



- 15 This compound was synthesized by the reaction of 5-{2-[(6-chloroquinolin-4-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl}-1-methyl-1H-pyrrole-3-carboxylic acid and ammonia using diethyl cyanophosphonate as a coupling reagent. Mass: 534.17 (M+H).

Example 62

5 **5-[2-(1-benzothien-3-ylmethyl)-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]-N-[2-(dimethylamino)ethyl]-1-methyl-1H-pyrrole-3-carboxamide**

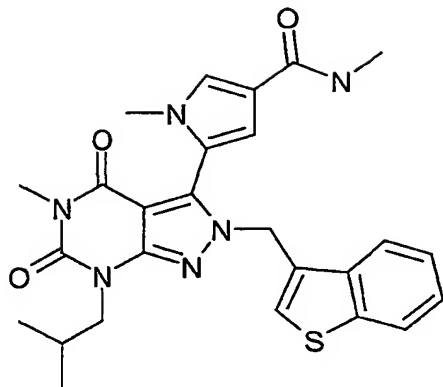


10 This compound was synthesized by the reaction of 5-[2-(1-benzothien-3-ylmethyl)-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]-1-methyl-1H-pyrrole-3-carboxylic acid and *N,N*-dimethylethane-1,2-diamine using diethyl cyanophosphonate as a coupling reagent. Mass: 562.18 (M+H).

15 **Example 63**

5-[2-(1-benzothien-3-ylmethyl)-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]-N,1-dimethyl-1H-pyrrole-3-carboxamide

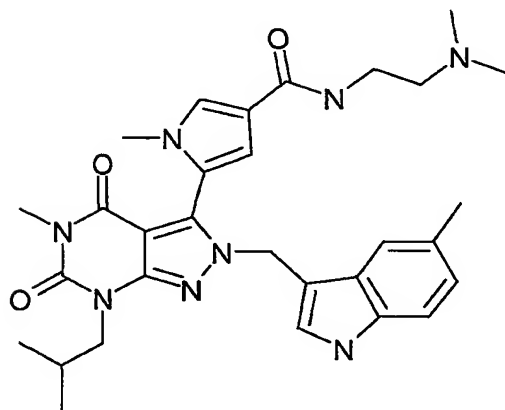
- 65 -



This compound was synthesized by the reaction of 5-[2-(1-benzothien-3-ylmethyl)-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]-1-methyl-1H-pyrrole-3-carboxylic acid and ammonia using diethyl cyanophosphonate as a coupling reagent. Mass: 505.13 (M+H).

Example 64

10 N-[2-(dimethylamino)ethyl]-5-{7-isobutyl-5-methyl-2-[(5-methyl-1H-indol-3-yl)methyl]-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl}-1-methyl-1H-pyrrole-3-carboxamide



15

This compound was synthesized by the reaction of 5-{7-isobutyl-5-methyl-2-[(5-methyl-1H-indol-3-yl)methyl]-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl}-1-methyl-1H-pyrrole-3-carboxylic acid and ammonia using diethyl cyanophosphonate as a coupling reagent. Mass: 505.13 (M+H).

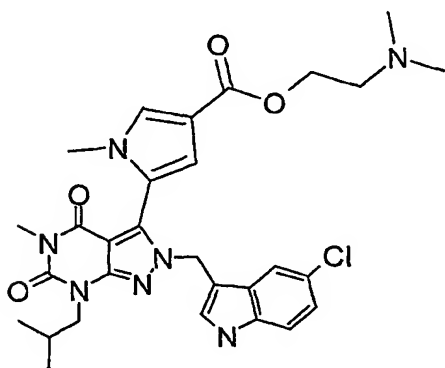
- 66 -

methyl-1*H*-pyrrole-3-carboxylic acid and *N,N*-dimethylethane-1,2-diamine using diethyl cyanophosphonate as a coupling reagent. Mass: 559.35 (M+H).

Example 65

5

2-(dimethylamino)ethyl 5-{2-[(5-chloro-1*H*-indol-3-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-1-methyl-1*H*-pyrrole-3-carboxylate



10

This compound was synthesized by the reaction of 5-{2-[(5-chloro-1*H*-indol-3-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-1-methyl-1*H*-pyrrole-3-carboxylic acid and 2-(dimethylamino)ethanol using PyBOP as a coupling reagent. Mass: 580.08 (M+H).

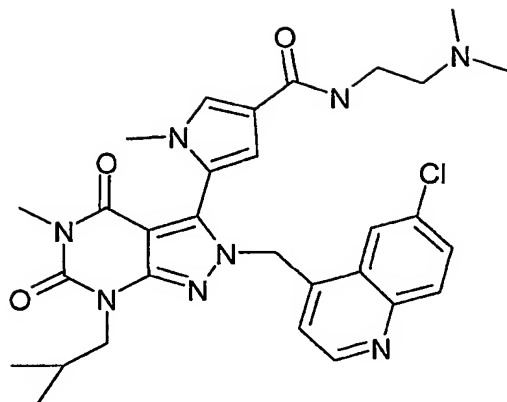
15

Example 66

5-{2-[(6-chloroquinolin-4-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-N-[2-(dimethylamino)ethyl]-1-methyl-1*H*-pyrrole-3-carboxamide

20

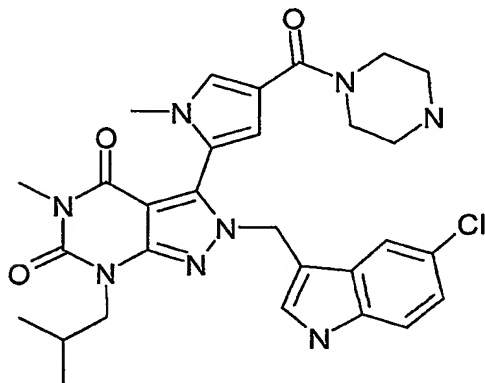
- 67 -



This compound was synthesized by the reaction of 5-{2-[(6-chloroquinolin-4-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl}-1-methyl-1H-pyrrole-3-carboxylic acid and *N,N*-dimethylethane-1,2-diamine using diethyl cyanophosphonate as a coupling reagent. Mass: 591.27 (M+H).

Example 67

2-[(5-chloro-1H-indol-3-yl)methyl]-7-isobutyl-5-methyl-3-[1-methyl-4-(piperazin-1-ylcarbonyl)-1H-pyrrol-2-yl]-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione



This compound was synthesized by the reaction of 5-{2-[(5-chloro-1H-indol-3-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl}-1-methyl-

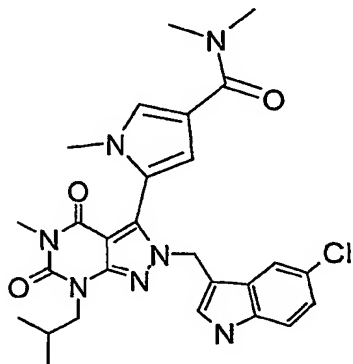
- 68 -

1*H*-pyrrole-3-carboxylic acid and piperazine using diethyl cyanophosphonate as a coupling reagent. Mass: 577.17 (M+H).

Example 68

5

5-{2-[(5-chloro-1*H*-indol-3-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-*N,N*,1-trimethyl-1*H*-pyrrole-3-carboxamide

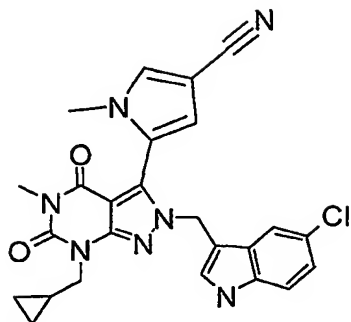


- 10 This compound was synthesized by the reaction of 5-{2-[(5-chloro-1*H*-indol-3-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-1-methyl-1*H*-pyrrole-3-carboxylic acid and dimethylamine using diethyl cyanophosphonate as a coupling reagent. Mass: 536.03 (M+H).

Example 69

5-[2-[(5-chloro-1*H*-indol-3-yl)methyl]-7-(cyclopropylmethyl)-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-1-methyl-1*H*-pyrrole-3-carbonitrile

- 69 -



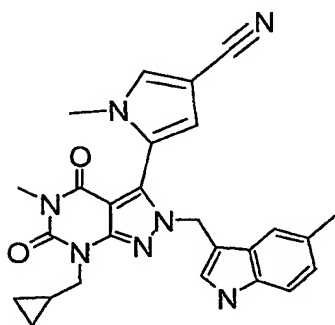
This compound was made following the procedure described above, starting with 1-

- 5 (cyclopropylmethyl)-6-hydrazino-3-methylpyrimidine-2,4(1*H*,3*H*)-dione, and condensing first with 5-chloro-1*H*-indole-3-carbaldehyde, followed by 5-formyl-1-methyl-1*H*-pyrrole-3-carbonitrile. Mass: 488.16 (M+H).

Example 70

10

5-{7-(cyclopropylmethyl)-5-methyl-2-[(5-methyl-1*H*-indol-3-yl)methyl]-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-1-methyl-1*H*-pyrrole-3-carbonitrile



15

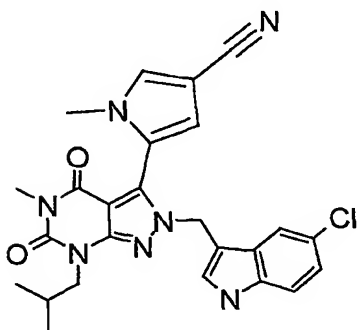
This compound was made following the procedure described above, starting with 1-

- 20 (cyclopropylmethyl)-6-hydrazino-3-methylpyrimidine-2,4(1*H*,3*H*)-dione, and condensing first with 5-methyl-1*H*-indole-3-carbaldehyde, followed by 5-formyl-1-methyl-1*H*-pyrrole-3-carbonitrile. Mass: 468.26 (M+H).

- 70 -

Example 71

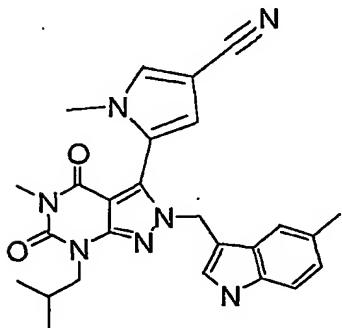
5-**{2-[(5-chloro-1H-indol-3-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-
2H-pyrazolo[3,4-d]pyrimidin-3-yl}-1-methyl-1H-pyrrole-3-carbonitrile**



- 10 This compound was made following the procedure described above, starting with 6-hydrazino-1-isobutyl-3-methylpyrimidine-2,4(1*H*,3*H*)-dione, and condensing first with 5-chloro-1*H*-indole-3-carbaldehyde, followed by 5-formyl-1-methyl-1*H*-pyrrole-3-carbonitrile. Mass: 490.16 (M+H).

15 **Example 72**

5-**{7-isobutyl-5-methyl-2-[(5-methyl-1H-indol-3-yl)methyl]-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl}-1-methyl-1H-pyrrole-3-carbonitrile**

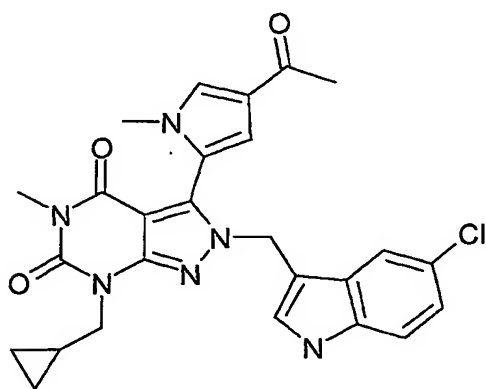


- 71 -

This compound was made following the procedure described above, starting with 6-hydrazino-1-isobutyl-3-methylpyrimidine-2,4(1*H*,3*H*)-dione, and condensing first with 5-methyl-1*H*-indole-3-carbaldehyde, followed by 5-formyl-1-methyl-1*H*-pyrrole-3-carbonitrile. Mass: 470.26 (M+H).

Example 73

10 3-(4-acetyl-1-methyl-1*H*-pyrrol-2-yl)-2-[(5-chloro-1*H*-indol-3-yl)methyl]-7-(cyclopropylmethyl)-5-methyl-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione



15

This compound was made following the procedure described above, starting with 1-(cyclopropylmethyl)-6-hydrazino-3-methylpyrimidine-2,4(1*H*,3*H*)-dione, and condensing first with 5-chloro-1*H*-indole-3-carbaldehyde, followed by 4-acetyl-1-methyl-1*H*-pyrrole-2-carbaldehyde. Mass: 505.12 (M+H).

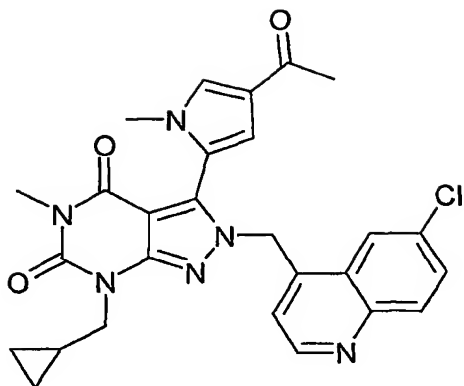
20

Example 74

25 3-(4-acetyl-1-methyl-1*H*-pyrrol-2-yl)-2-[(6-chloroquinolin-4-yl)methyl]-7-(cyclopropylmethyl)-5-methyl-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione

25

- 72 -

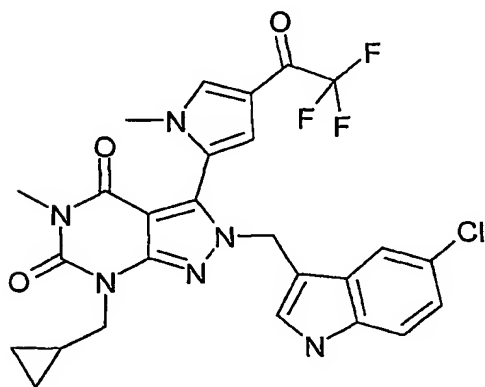


This compound was made following the procedure described above, starting with 1-
 5 (cyclopropylmethyl)-6-hydrazino-3-methylpyrimidine-2,4(1*H*,3*H*)-dione, and condensing
 first with 6-chloroquinoline-4-carbaldehyde, followed by 4-acetyl-1-methyl-1*H*-pyrrole-2-
 carbaldehyde. Mass: 517.14 (M+H).

Example 75

10

2-[(5-chloro-1*H*-indol-3-yl)methyl]-7-(cyclopropylmethyl)-5-methyl-3-[1-methyl-4-
 (trifluoroacetyl)-1*H*-pyrrol-2-yl]-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione



15

This compound was made following the procedure described above, starting with 1-
 (cyclopropylmethyl)-6-hydrazino-3-methylpyrimidine-2,4(1*H*,3*H*)-dione, and condensing

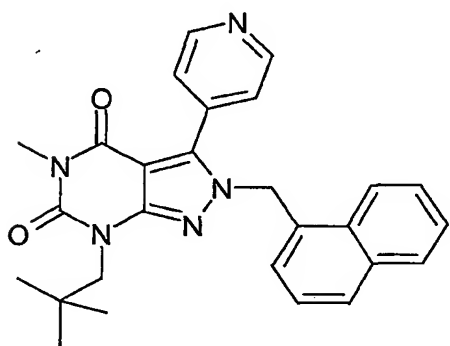
- 73 -

first with 5-chloro-1*H*-indole-3-carbaldehyde, followed by 1-methyl-4-(trifluoroacetyl)-1*H*-pyrrole-2-carbaldehyde. Mass: 559.15 (M+H).

Example 76

5

**5-methyl-2-(1-naphthylmethyl)-7-neopentyl-3-pyridin-4-yl-2*H*-pyrazolo[3,4-
d]pyrimidine-4,6(5*H*,7*H*)-dione**



10

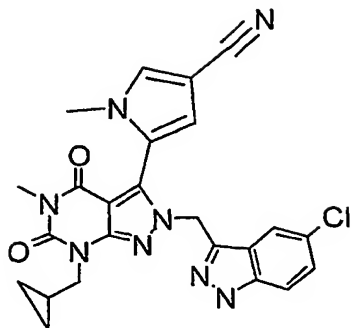
This compound was synthesized by the reaction of 5-methyl-2-(1-naphthylmethyl)-3-pyridin-4-yl-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione and 1-bromo-2-methylpropane using DBU as a base in DMF at 100°C. Mass: 454.36 (M+H).

15

Example 77

**5-[2-[(5-chloro-1*H*-indazol-3-yl)methyl]-7-(cyclopropylmethyl)-5-methyl-4,6-dioxo-
4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-1-methyl-1*H*-pyrrole-3-
20 carbonitrile**

- 74 -

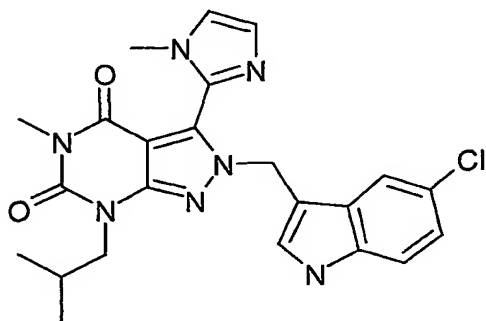


This compound was made following the procedure described above, starting with 1-
 5 (cyclopropylmethyl)-6-hydrazino-3-methylpyrimidine-2,4(1*H*,3*H*)-dione, and condensing
 first with 5-chloro-1*H*-indazole-3-carbaldehyde, followed by 5-formyl-1-methyl-1*H*-pyrrole-
 3-carbonitrile. Mass: 489.10 (M+H).

Example 78

10

2-[(5-chloro-1*H*-indol-3-yl)methyl]-7-isobutyl-5-methyl-3-(1-methyl-1*H*-imidazol-2-yl)-
 2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione



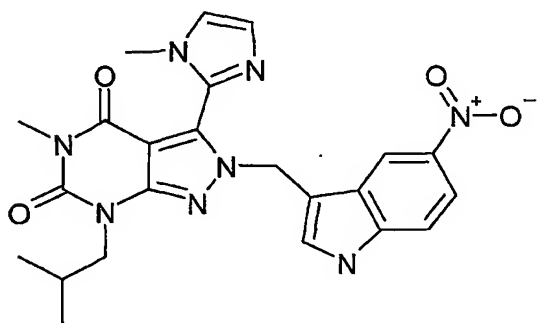
15

This compound was made following the procedure described above, starting with 6-
 hydrazino-1-isobutyl-3-methylpyrimidine-2,4(1*H*,3*H*)-dione, and condensing first with 5-
 chloro-1*H*-indole-3-carbaldehyde, followed by 1-methyl-1*H*-imidazole-2-carbaldehyde.
 20 Mass: 466.17 (M+H).

- 75 -

Example 79

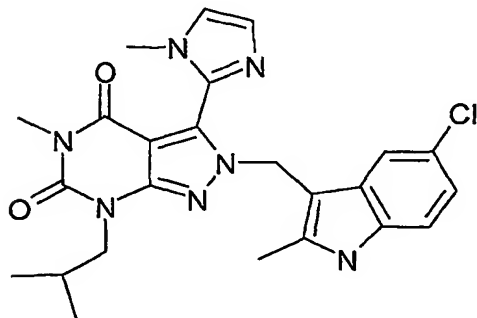
7-isobutyl-5-methyl-3-(1-methyl-1H-imidazol-2-yl)-2-[(5-nitro-1H-indol-3-yl)methyl]-
5 2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione



10 This compound was made following the procedure described above, starting with 6-hydrazino-1-isobutyl-3-methylpyrimidine-2,4(1H,3H)-dione, and condensing first with 5-nitro-1H-indole-3-carbaldehyde, followed by 1-methyl-1H-imidazole-2-carbaldehyde. Mass: 477.19 (M+H).

15 **Example 80**

2-[(5-chloro-2-methyl-1H-indol-3-yl)methyl]-7-isobutyl-5-methyl-3-(1-methyl-1H-imidazol-2-yl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione

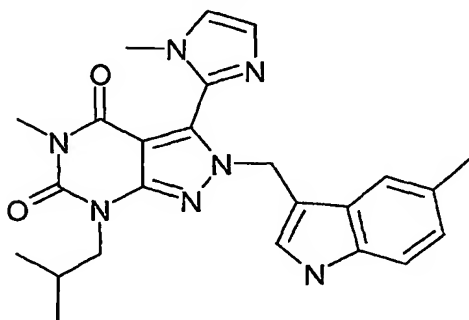


20

- This compound was made following the procedure described above, starting with 6-hydrazino-1-isobutyl-3-methylpyrimidine-2,4(1*H*,3*H*)-dione, and condensing first with 5-chloro-2-methyl-1*H*-indole-3-carbaldehyde, followed by 1-methyl-1*H*-imidazole-2-carbaldehyde. Mass: 480.10 (M+H).

Example 81

- 10 7-isobutyl-5-methyl-3-(1-methyl-1*H*-imidazol-2-yl)-2-[(5-methyl-1*H*-indol-3-yl)methyl]-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione

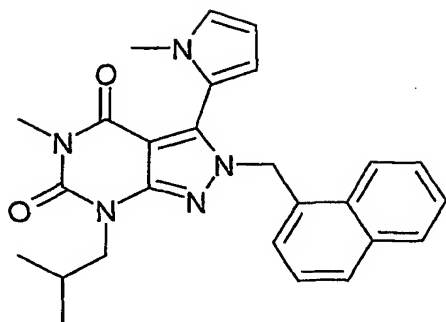


- 15 This compound was made following the procedure described above, starting with 6-hydrazino-1-isobutyl-3-methylpyrimidine-2,4(1*H*,3*H*)-dione, and condensing first with 5-methyl-1*H*-indole-3-carbaldehyde, followed by 1-methyl-1*H*-imidazole-2-carbaldehyde. Mass: 446.26 (M+H).

20 **Example 82**

7-isobutyl-5-methyl-3-(1-methyl-1*H*-pyrrol-2-yl)-2-(1-naphthylmethyl)-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione

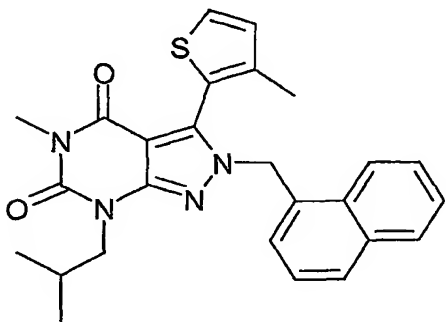
- 77 -



This compound was made following the procedure described above, starting with 6-hydrazino-1-isobutyl-3-methylpyrimidine-2,4(1*H*,3*H*)-dione, and condensing first with 1-naphthaldehyde, followed by 1-methyl-1*H*-pyrrole-2-carbaldehyde. Mass: 442.35 (M+H).

Example 83

10 **7-isobutyl-5-methyl-3-(3-methylthien-2-yl)-2-(1-naphthylmethyl)-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione**

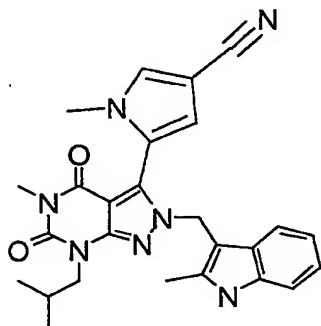


15 This compound was made following the procedure described above, starting with 6-hydrazino-1-isobutyl-3-methylpyrimidine-2,4(1*H*,3*H*)-dione, and condensing first with 1-naphthaldehyde, followed by 3-methylthiophene-2-carbaldehyde. Mass: 458.87 (M+H).

Example 84

- 78 -

5-**{7-isobutyl-5-methyl-2-[(2-methyl-1H-indol-3-yl)methyl]-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl}-1-methyl-1H-pyrrole-3-carbonitrile**



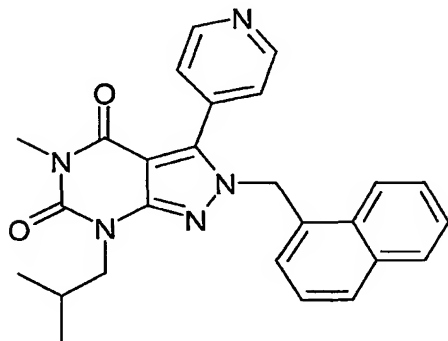
5

This compound was made following the procedure described above, starting with 6-hydrazino-1-isobutyl-3-methylpyrimidine-2,4(1*H*,3*H*)-dione, and condensing first with 2-methyl-1*H*-indole-3-carbaldehyde, followed by 5-formyl-1-methyl-1*H*-pyrrole-3-carbonitrile.

10 Mass: 470.20 (M+H).

Example 85

15 **7-isobutyl-5-methyl-2-(1-naphthylmethyl)-3-pyridin-4-yl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5*H*,7*H*)-dione**

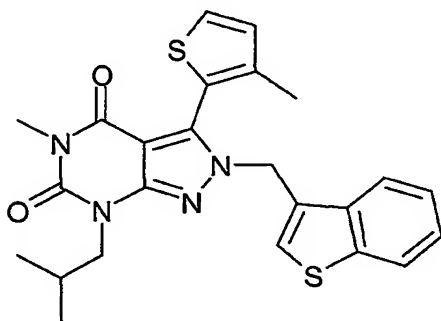


- 79 -

This compound was made following the procedure described above, starting with 6-hydrazino-1-isobutyl-3-methylpyrimidine-2,4(1*H*,3*H*)-dione, and condensing first with 1-naphthaldehyde, followed by isonicotinaldehyde. Mass: 439.79 (M+H).

5 Example 86

2-(1-benzothien-3-ylmethyl)-7-isobutyl-5-methyl-3-(3-methylthien-2-yl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5*H*,7*H*)-dione



10

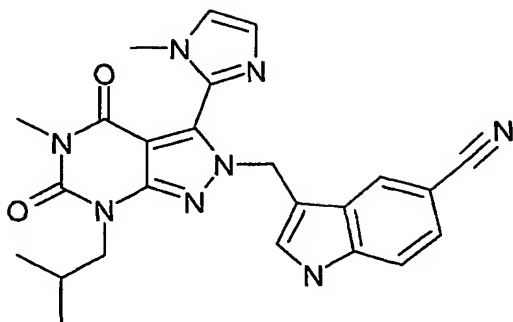
This compound was made following the procedure described above, starting with 6-hydrazino-1-isobutyl-3-methylpyrimidine-2,4(1*H*,3*H*)-dione, and condensing first with 1-benzothiophene-3-carbaldehyde, followed by 3-methylthiophene-2-carbaldehyde. Mass: 464.85 (M+H).

15

Example 87

20 3-{[7-isobutyl-5-methyl-3-(1-methyl-1*H*-imidazol-2-yl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-2-yl]methyl}-1*H*-indole-5-carbonitrile

- 80 -

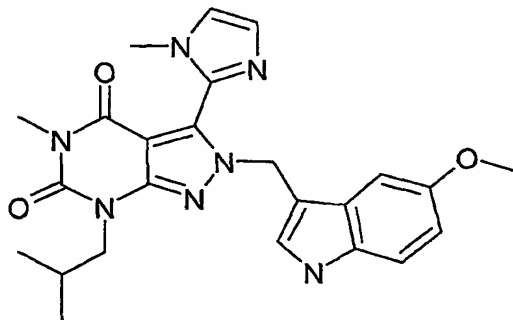


This compound was made following the procedure described above, starting with 6-
5 hydrazino-1-isobutyl-3-methylpyrimidine-2,4(1*H*,3*H*)-dione, and condensing first with 3-
formyl-1*H*-indole-5-carbonitrile, followed by 1-methyl-1*H*-imidazole-2-carbaldehyde. Mass:
457.14 (M+H).

Example 88

10

7-isobutyl-2-[(5-methoxy-1*H*-indol-3-yl)methyl]-5-methyl-3-(1-methyl-1*H*-imidazol-2-
yl)-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione



15

This compound was made following the procedure described above, starting with 6-
hydrazino-1-isobutyl-3-methylpyrimidine-2,4(1*H*,3*H*)-dione, and condensing first with 5-
methoxy-1*H*-indole-3-carbaldehyde, followed by 1-methyl-1*H*-imidazole-2-carbaldehyde.
Mass: 462.21 (M+H).

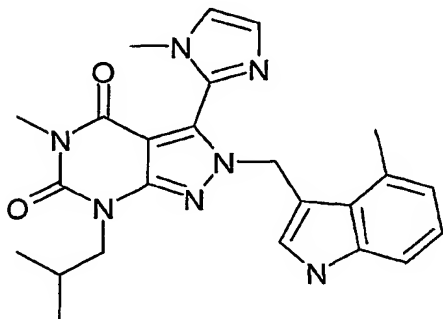
20

- 81 -

Example 89

7-isobutyl-5-methyl-3-(1-methyl-1H-imidazol-2-yl)-2-[(4-methyl-1H-indol-3-yl)methyl]-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione

5

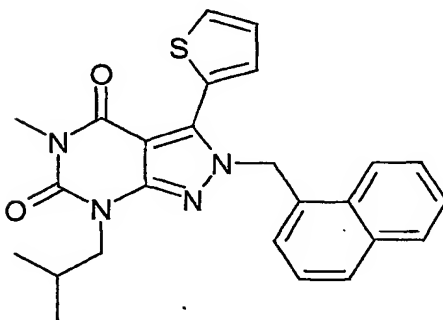


This compound was made following the procedure described above, starting with 6-hydrazino-1-isobutyl-3-methylpyrimidine-2,4(1H,3H)-dione, and condensing first with 4-methyl-1H-indole-3-carbaldehyde, followed by 1-methyl-1H-imidazole-2-carbaldehyde. Mass: 446.45 (M+H).

Example 90

15

7-isobutyl-5-methyl-2-(1-naphthylmethyl)-3-thien-2-yl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione



20

- 82 -

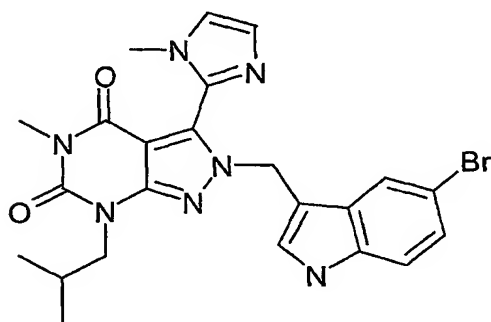
This compound was made following the procedure described above, starting with 6-hydrazino-1-isobutyl-3-methylpyrimidine-2,4(1*H*,3*H*)-dione, and condensing first with 1-naphthaldehyde, followed by thiophene-2-carbaldehyde. Mass: 444.88 (M+H).

5

Example 91

2-[(5-bromo-1*H*-indol-3-yl)methyl]-7-isobutyl-5-methyl-3-(1-methyl-1*H*-imidazol-2-yl)-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione

10



This compound was made following the procedure described above, starting with 6-hydrazino-1-isobutyl-3-methylpyrimidine-2,4(1*H*,3*H*)-dione, and condensing first with 5-bromo-1*H*-indole-3-carbaldehyde, followed by 1-methyl-1*H*-imidazole-2-carbaldehyde.

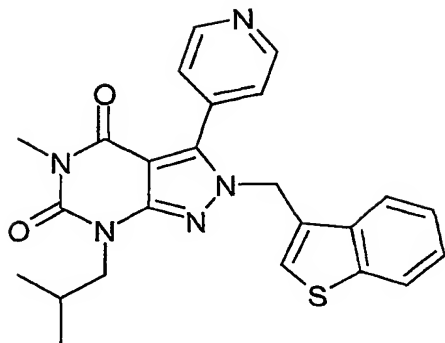
15

Example 92

2-(1-benzothien-3-ylmethyl)-7-isobutyl-5-methyl-3-pyridin-4-yl-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione

20

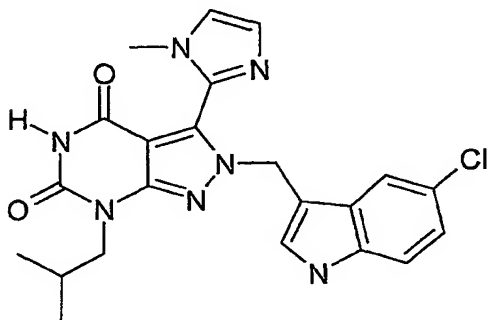
- 83 -



This compound was made following the procedure described above, starting with 6-hydrazino-1-isobutyl-3-methylpyrimidine-2,4(1*H*,3*H*)-dione, and condensing first with 1-benzothiophene-3-carbaldehyde, followed by isonicotinaldehyde. Mass: 445.92 (M+H).

Example 93

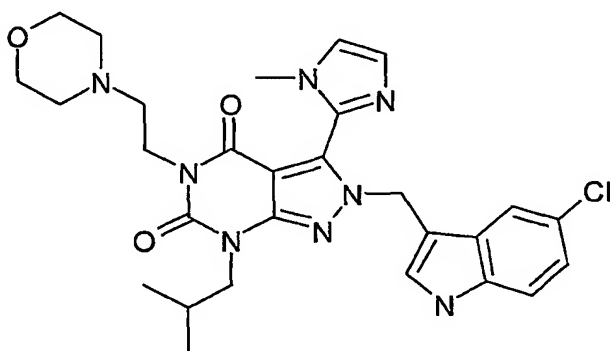
2-[(5-chloro-1*H*-indol-3-yl)methyl]-7-isobutyl-3-(1-methyl-1*H*-imidazol-2-yl)-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione



This compound was made following the procedure described above, starting with 6-hydrazino-1-isobutylpyrimidine-2,4(1*H*,3*H*)-dione, and condensing first with 5-chloro-1*H*-indole-3-carbaldehyde, followed by 1-methyl-1*H*-imidazole-2-carbaldehyde. Mass: 452.18 (M+H).

Example 94

2-[(5-chloro-1H-indol-3-yl)methyl]-7-isobutyl-3-(1-methyl-1H-imidazol-2-yl)-5-(2-morpholin-4-ylethyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione



5

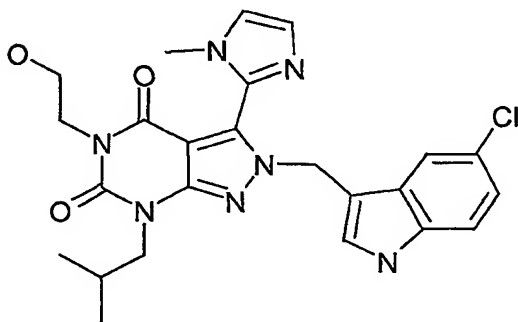
This compound was synthesized by the reaction of 2-[(5-chloro-1H-indol-3-yl)methyl]-7-isobutyl-3-(1-methyl-1H-imidazol-2-yl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione and 4-(2-chloroethyl)morpholine using potassium carbonate as a base. Mass: 565.17 (M+H).

10

Example 95

2-[(5-chloro-1H-indol-3-yl)methyl]-5-(2-hydroxyethyl)-7-isobutyl-3-(1-methyl-1H-imidazol-2-yl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione

15

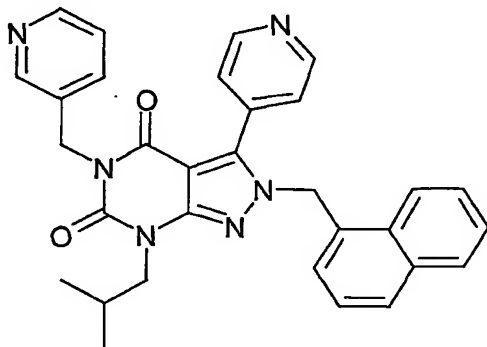


This compound was synthesized by the reaction of 2-[(5-chloro-1H-indol-3-yl)methyl]-7-isobutyl-3-(1-methyl-1H-imidazol-2-yl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione and 2-bromoethanol using potassium carbonate as a base. Mass: 496.17 (M+H).

20

Example 96

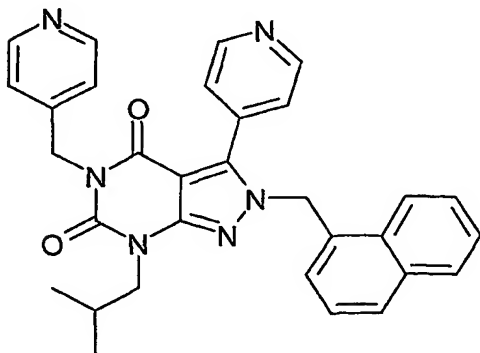
7-isobutyl-2-(1-naphthylmethyl)-3-pyridin-4-yl-5-(pyridin-3-ylmethyl)-2H-pyrazolo[3,4-
5 d]pyrimidine-4,6(5H,7H)-dione



This compound was synthesized by the reaction of 7-isobutyl-2-(1-naphthylmethyl)-3-pyridin-4-yl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione and 3-(chloromethyl)pyridine
10 hydrochloride using DBU as a base. Mass: 516.86 (M+H).

Example 97

7-isobutyl-2-(1-naphthylmethyl)-3-pyridin-4-yl-5-(pyridin-4-ylmethyl)-2H-pyrazolo[3,4-
15 d]pyrimidine-4,6(5H,7H)-dione

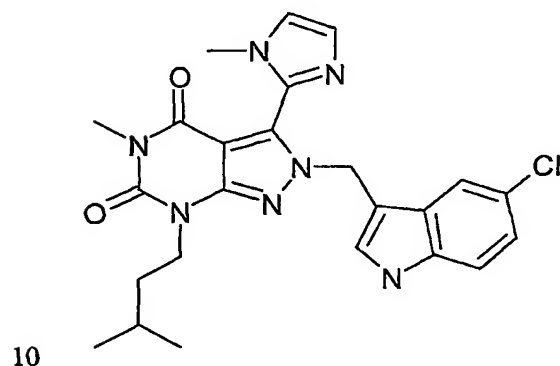


- 86 -

This compound was synthesized by the reaction of 7-isobutyl-2-(1-naphthylmethyl)-3-pyridin-4-yl-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione and 4-(chloromethyl)pyridine hydrochloride using DBU as a base. Mass: 516.88 (M+H).

5 Example 98

2-[(5-chloro-1*H*-indol-3-yl)methyl]-5-methyl-7-(3-methylbutyl)-3-(1-methyl-1*H*-imidazol-2-yl)-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione



(a) 2-[(5-chloro-1*H*-indol-3-yl)methyl]-5-methyl-3-(1-methyl-1*H*-imidazol-2-yl)-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione

This compound was made following the procedure described above, starting with 6-hydrazino-3-methylpyrimidine-2,4(1*H*,3*H*)-dione, and condensing first with 5-chloro-1*H*-indole-3-carbaldehyde, followed by 1-methyl-1*H*-imidazole-2-carbaldehyde

15

(b) 2-[(5-chloro-1*H*-indol-3-yl)methyl]-5-methyl-7-(3-methylbutyl)-3-(1-methyl-1*H*-imidazol-2-yl)-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione

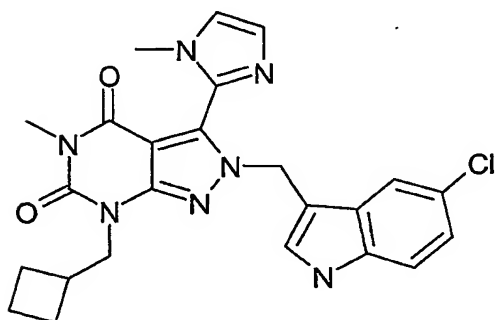
This compound was synthesized by the reaction of 2-[(5-chloro-1*H*-indol-3-yl)methyl]-5-methyl-3-(1-methyl-1*H*-imidazol-2-yl)-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione and 1-bromo-3-methylbutane using potassium carbonate as a base in DMF at 80°C. Mass: 480.16 (M+H).

20

25 Example 99

- 87 -

2-[(5-chloro-1*H*-indol-3-yl)methyl]-7-(cyclobutylmethyl)-5-methyl-3-(1-methyl-1*H*-imidazol-2-yl)-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione



5

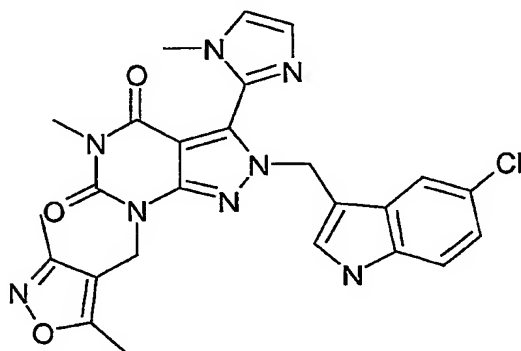
This compound was synthesized by the reaction of 2-[(5-chloro-1*H*-indol-3-yl)methyl]-5-methyl-3-(1-methyl-1*H*-imidazol-2-yl)-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione and (bromomethyl)cyclobutane using potassium carbonate as a base in DMF at 80°C. Mass:

10 478.16 (M+H).

Example 100

2-[(5-chloro-1*H*-indol-3-yl)methyl]-7-[(3,5-dimethylisoxazol-4-yl)methyl]-5-methyl-3-(1-methyl-1*H*-imidazol-2-yl)-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione

15



This compound was synthesized by the reaction of 2-[(5-chloro-1*H*-indol-3-yl)methyl]-5-methyl-3-(1-methyl-1*H*-imidazol-2-yl)-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione and

20

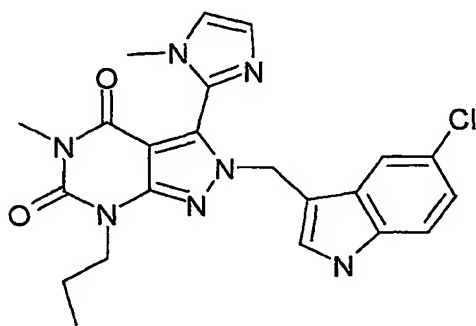
- 88 -

4-(bromomethyl)-3,5-dimethylisoxazole using potassium carbonate as a base in DMF at 80°C.
Mass: 519.01 (M+H).

Example 101

5

2-[(5-chloro-1H-indol-3-yl)methyl]-5-methyl-3-(1-methyl-1H-imidazol-2-yl)-7-propyl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione



10

This compound was synthesized by the reaction of 2-[(5-chloro-1H-indol-3-yl)methyl]-5-methyl-3-(1-methyl-1H-imidazol-2-yl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione and 1-bromopropane using potassium carbonate as a base in DMF at 80°C. Mass: 452.08 (M+H).

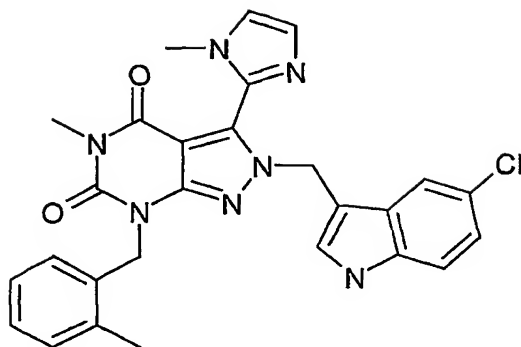
15

Example 102

2-[(5-chloro-1H-indol-3-yl)methyl]-5-methyl-7-(2-methylbenzyl)-3-(1-methyl-1H-imidazol-2-yl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione

20

- 89 -

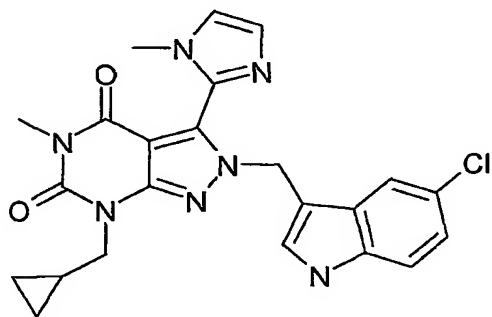


This compound was synthesized by the reaction of 2-[(5-chloro-1*H*-indol-3-yl)methyl]-5-methyl-3-(1-methyl-1*H*-imidazol-2-yl)-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione and 1-(bromomethyl)-2-methylbenzene using DBU as a base in DMF at 80°C. Mass: 514.11 (M+H).

Example 103

10

2-[(5-chloro-1*H*-indol-3-yl)methyl]-5-methyl-3-(1-methyl-1*H*-imidazol-2-yl)-7-propyl-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione



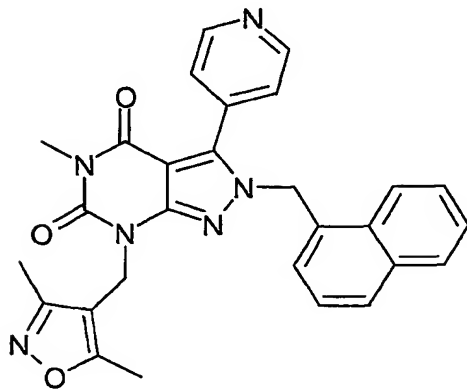
15

This compound was synthesized by the reaction of 2-[(5-chloro-1*H*-indol-3-yl)methyl]-5-methyl-3-(1-methyl-1*H*-imidazol-2-yl)-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione and (bromomethyl)cyclopropane using potassium carbonate as a base in DMF at 80°C. Mass: 464.14 (M+H).

20

Example 104

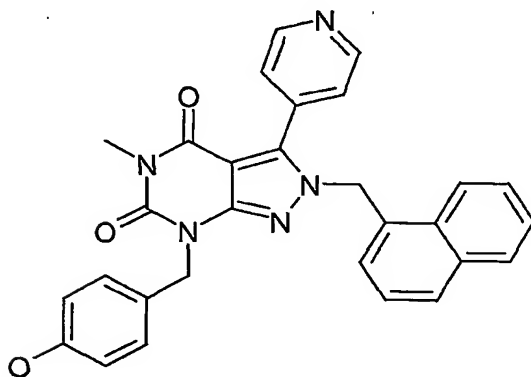
7-[(3,5-dimethylisoxazol-4-yl)methyl]-5-methyl-2-(1-naphthylmethyl)-3-pyridin-4-yl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione



This compound was synthesized by the reaction of 5-methyl-2-(1-naphthylmethyl)-3-pyridin-4-yl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione and 4-(bromomethyl)-3,5-dimethylisoxazole using potassium carbonate as a base in DMF at 80°C. Mass: 492.94 (M+H).

Example 105

7-(4-hydroxybenzyl)-5-methyl-2-(1-naphthylmethyl)-3-pyridin-4-yl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione



- 91 -

(a) 4-{[5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-3-pyridin-4-yl-2,4,5,6-tetrahydro-7H-pyrazolo[3,4-*d*]pyrimidin-7-yl]methyl}phenyl acetate

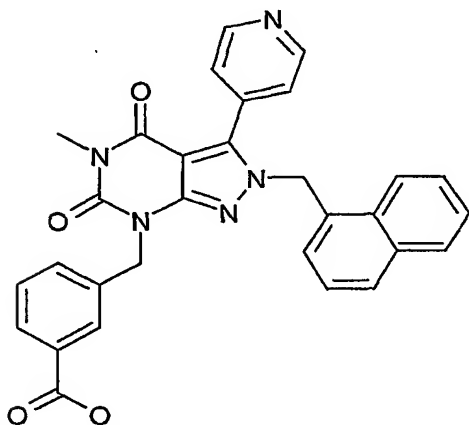
This compound was synthesized by the reaction of 5-methyl-2-(1-naphthylmethyl)-3-pyridin-4-yl-2H-pyrazolo[3,4-*d*]pyrimidine-4,6(5H,7H)-dione and 4-(chloromethyl)phenyl acetate using potassium carbonate as a base in DMF at 80°C.

(b) 7-(4-hydroxybenzyl)-5-methyl-2-(1-naphthylmethyl)-3-pyridin-4-yl-2H-pyrazolo[3,4-*d*]pyrimidine-4,6(5H,7H)-dione

This compound was synthesized by the hydrolysis of 4-{[5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-3-pyridin-4-yl-2,4,5,6-tetrahydro-7H-pyrazolo[3,4-*d*]pyrimidin-7-yl]methyl}phenyl acetate with 0.5N LiOH at room temperature for six hours. Mass: 489.80 (M+H).

Example 106

3-{[5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-3-pyridin-4-yl-2,4,5,6-tetrahydro-7H-pyrazolo[3,4-*d*]pyrimidin-7-yl]methyl}benzoic acid



(a) methyl 3-{[5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-3-pyridin-4-yl-2,4,5,6-tetrahydro-7H-pyrazolo[3,4-*d*]pyrimidin-7-yl]methyl}benzoate

This compound was synthesized by the reaction of 5-methyl-2-(1-naphthylmethyl)-3-pyridin-4-yl-2H-pyrazolo[3,4-*d*]pyrimidine-4,6(5H,7H)-dione and methyl 3-(bromomethyl)benzoate using potassium carbonate as a base in DMF at 80°C.

- 92 -

(b) 3-{[5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-3-pyridin-4-yl-2,4,5,6-tetrahydro-7H-pyrazolo[3,4-d]pyrimidin-7-yl]methyl}benzoic acid

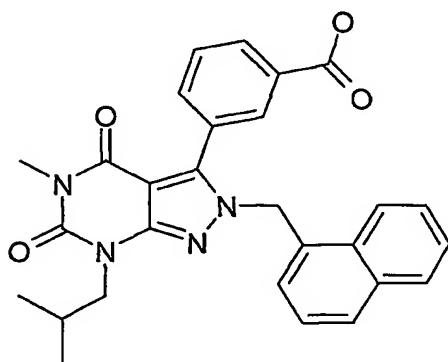
This compound was synthesized by the hydrolysis of methyl 3-{[5-methyl-2-(1-

- 5 naphthylmethyl)-4,6-dioxo-3-pyridin-4-yl-2,4,5,6-tetrahydro-7H-pyrazolo[3,4-d]pyrimidin-7-yl]methyl}benzoate with 0.5N LiOH at room temperature for eight hours. Mass: 517.79 (M+H).

Example 107

10

3-[7-isobutyl-5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]benzoic acid



15

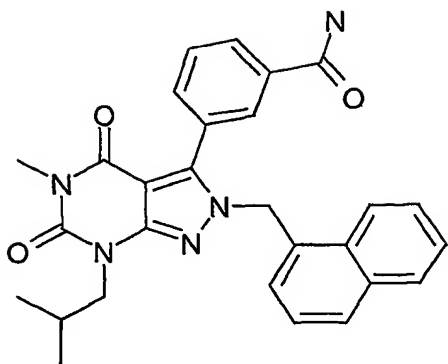
This compound was made following the procedure described above, starting with 6-hydrazino-1-isobutyl-3-methylpyrimidine-2,4(1*H*,3*H*)-dione, and condensing first with 1-naphthaldehyde, followed by 3-formylbenzoic acid. Mass: 482.72 (M+H).

Example 108

20

3-[7-isobutyl-5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]benzamide

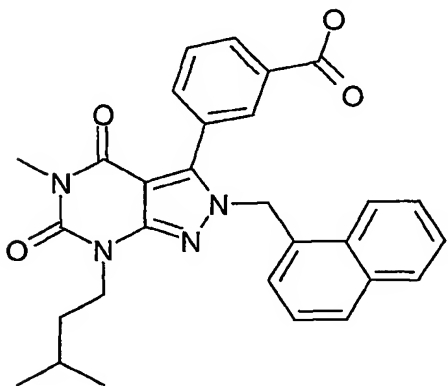
- 93 -



This compound was synthesized by the reaction of 3-[7-isobutyl-5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]benzoic acid
 5 and ammonia in water using diethyl isobutyl chloroformate as a coupling reagent. Mass: 481.89 (M+H).

Example 109

10 3-[5-methyl-7-(3-methylbutyl)-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]benzoic acid



(a) Resin bound 3-[5-methyl-7-(3-methylbutyl)-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]benzoic acid
 15

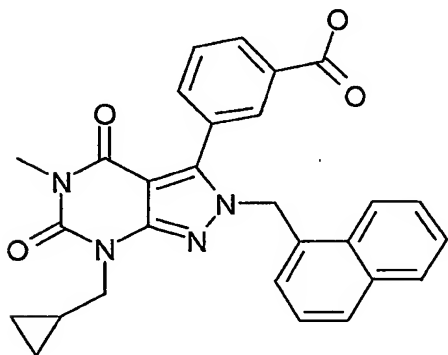
This compound was synthesized by the reaction of resin bound 3-[5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]benzoic acid and 1-bromo-3-methylbutane using potassium carbonate as a base in DMF at 85°C.

(b) 3-[5-methyl-7-(3-methylbutyl)-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]benzoic acid

This compound was synthesized by treating resin bound 3-[5-methyl-7-(3-methylbutyl)-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]benzoic acid
 5 with 15% TFA in dichloromethane at room temperature for 2 hours. Mass: 496.92 (M+H).

Example 110

10 3-[7-(cyclopropylmethyl)-5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]benzoic acid



15

(a) Resin bound 3-[7-(cyclopropylmethyl)-5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]benzoic acid

This compound was synthesized by the reaction of resin bound 3-[5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]benzoic acid
 20 and (bromomethyl)cyclopropane using potassium carbonate as a base in DMF at 85°C.

(b) 3-[7-(cyclopropylmethyl)-5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]benzoic acid

This compound was synthesized by treating resin bound 3-[7-(cyclopropylmethyl)-5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]benzoic
 25

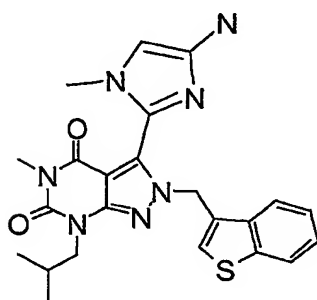
- 95 -

acid with 15% TFA in dichloromethane at room temperature for 2 hours. Mass: 480.93 (M+H).

Example 111

5

3-(4-amino-1-methyl-1H-imidazol-2-yl)-2-(1-benzothien-3-ylmethyl)-7-isobutyl-5-methyl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione



10

(a) *tert*-butyl 2-[2-(1-benzothien-3-ylmethyl)-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-*d*]pyrimidin-3-yl]-1-methyl-1H-imidazol-4-ylcarbamate

This compound was made following the procedure described above, starting with 6-

15 hydrazino-1-isobutyl-3-methylpyrimidine-2,4(1*H*,3*H*)-dione, and condensing first with 1-benzothiophene-3-carbaldehyde, followed by *tert*-butyl 2-formyl-1-methyl-1*H*-imidazol-4-ylcarbamate.

20 **(b) 3-(4-amino-1-methyl-1H-imidazol-2-yl)-2-(1-benzothien-3-ylmethyl)-7-isobutyl-5-methyl-2H-pyrazolo[3,4-*d*]pyrimidine-4,6(5H,7H)-dione**

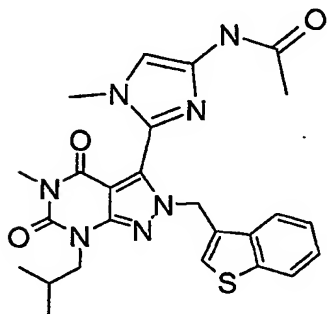
This compound was synthesized by treating *tert*-butyl 2-[2-(1-benzothien-3-ylmethyl)-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-*d*]pyrimidin-3-yl]-1-methyl-1*H*-imidazol-4-ylcarbamate with 4M HCl in dioxane at room temperature for 3 hours. Mass: 464.10 (M+H).

25

Example 112

- 96 -

N-{2-[2-(1-benzothien-3-ylmethyl)-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-1-methyl-1*H*-imidazol-4-yl}acetamide



5

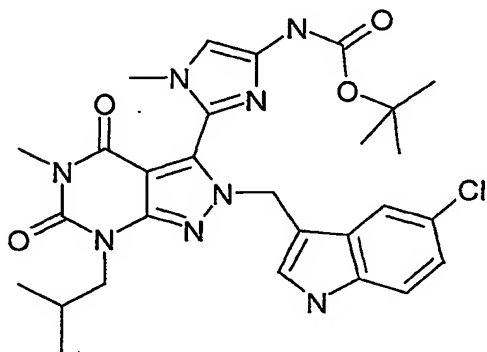
This compound was synthesized by the reaction of 3-(4-amino-1-methyl-1*H*-imidazol-2-yl)-2-(1-benzothien-3-ylmethyl)-7-isobutyl-5-methyl-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione hydrochloride and acetyl chloride using triethylamine as a base. Mass: 506.09 (M+H).

10

Example 113

tert-butyl 2-{2-[(5-chloro-1*H*-indol-3-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-1-methyl-1*H*-imidazol-4-ylcarbamate

15



This compound was made following the procedure described above, starting with 6-hydrazino-1-isobutylpyrimidine-2,4(1*H*,3*H*)-dione, and condensing first with 5-chloro-1*H*-

20

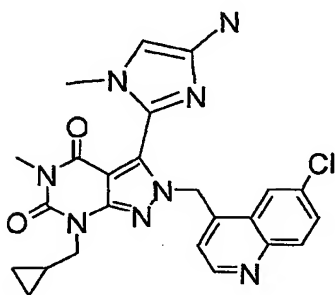
- 97 -

indole-3-carbaldehyde, followed by *tert*-butyl 2-formyl-1-methyl-1*H*-imidazol-4-ylcarbamate.
Mass: 581.03 (M+H).

Example 114

5

3-(4-amino-1-methyl-1*H*-imidazol-2-yl)-2-[(6-chloroquinolin-4-yl)methyl]-7-(cyclopropylmethyl)-5-methyl-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione



10

(a) *tert*-butyl 2-[2-[(6-chloroquinolin-4-yl)methyl]-7-(cyclopropylmethyl)-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-1-methyl-1*H*-imidazol-4-ylcarbamate

15 This compound was made following the procedure described above, starting with 1-(cyclopropylmethyl)-6-hydrazino-3-methylpyrimidine-2,4(1*H*,3*H*)-dione, and condensing first with 6-chloroquinoline-4-carbaldehyde, followed by *tert*-butyl 2-formyl-1-methyl-1*H*-imidazol-4-ylcarbamate.

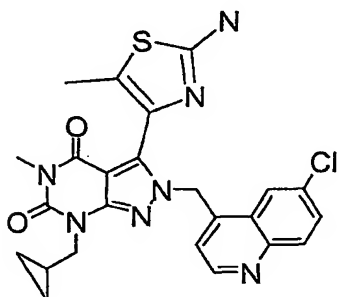
20 **(b) 3-(4-amino-1-methyl-1*H*-imidazol-2-yl)-2-[(6-chloroquinolin-4-yl)methyl]-7-(cyclopropylmethyl)-5-methyl-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione**

This compound was synthesized by treating *tert*-butyl 2-[2-[(6-chloroquinolin-4-yl)methyl]-7-(cyclopropylmethyl)-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-1-methyl-1*H*-imidazol-4-ylcarbamate with 10% TFA in dichloromethane at room
25 temperature for 5 hours. Mass: 491.26 (M+H).

Example 115

- 98 -

3-(2-amino-5-methyl-1,3-thiazol-4-yl)-2-[(6-chloroquinolin-4-yl)methyl]-7-(cyclopropylmethyl)-5-methyl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione



5

(a) *tert*-butyl 4-[2-[(6-chloroquinolin-4-yl)methyl]-7-(cyclopropylmethyl)-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]-5-methyl-1,3-thiazol-2-ylcarbamate

10

This compound was made following the procedure described above, starting with 1-(cyclopropylmethyl)-6-hydrazino-3-methylpyrimidine-2,4(1H,3H)-dione, and condensing first with 6-chloroquinoline-4-carbaldehyde, followed by *tert*-butyl 4-formyl-5-methyl-1,3-thiazol-2-ylcarbamate.

15

(b) 3-(2-amino-5-methyl-1,3-thiazol-4-yl)-2-[(6-chloroquinolin-4-yl)methyl]-7-(cyclopropylmethyl)-5-methyl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione

This compound was synthesized by treating *tert*-butyl 4-[2-[(6-chloroquinolin-4-yl)methyl]-7-(cyclopropylmethyl)-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]-5-methyl-1,3-thiazol-2-ylcarbamate with 10% TFA in dichloromethane at room temperature for 5 hours. Mass: 508.13 (M+H).

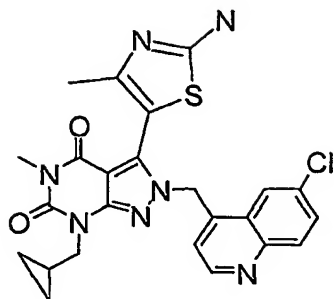
20

Example 116

3-(2-amino-4-methyl-1,3-thiazol-5-yl)-2-[(6-chloroquinolin-4-yl)methyl]-7-(cyclopropylmethyl)-5-methyl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione

25

- 99 -



(a) *tert*-butyl 5-[2-[(6-chloroquinolin-4-yl)methyl]-7-(cyclopropylmethyl)-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-4-methyl-1,3-thiazol-2-ylcarbamate

This compound was made following the procedure described above, starting with 1-(cyclopropylmethyl)-6-hydrazino-3-methylpyrimidine-2,4(1*H*,3*H*)-dione, and condensing first with 6-chloroquinoline-4-carbaldehyde, followed by *tert*-butyl 5-formyl-4-methyl-1,3-thiazol-2-ylcarbamate.

(b) 3-(2-amino-4-methyl-1,3-thiazol-5-yl)-2-[(6-chloroquinolin-4-yl)methyl]-7-(cyclopropylmethyl)-5-methyl-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione

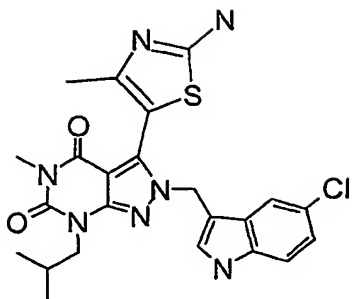
This compound was synthesized by treating *tert*-butyl 5-[2-[(6-chloroquinolin-4-yl)methyl]-7-(cyclopropylmethyl)-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-4-methyl-1,3-thiazol-2-ylcarbamate with 10% TFA in dichloromethane at room temperature for 5 hours. Mass: 508.13 (M+H).

Example 117

20

3-(2-amino-4-methyl-1,3-thiazol-5-yl)-2-[(5-chloro-1*H*-indol-3-yl)methyl]-7-isobutyl-5-methyl-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione

- 100 -

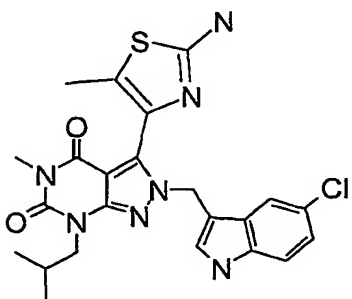


This compound was made following the procedure described above, starting with 6-hydrazino-1-isobutylpyrimidine-2,4(1*H*,3*H*)-dione, and condensing first with 5-chloro-1*H*-indole-3-carbaldehyde, followed by 2-amino-4-methyl-1,3-thiazole-5-carbaldehyde hydrochloride. Mass: 498.17 (M+H).

Example 118

10

3-(2-amino-5-methyl-1,3-thiazol-4-yl)-2-[(5-chloro-1*H*-indol-3-yl)methyl]-7-isobutyl-5-methyl-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione



15

This compound was made following the procedure described above, starting with 6-hydrazino-1-isobutylpyrimidine-2,4(1*H*,3*H*)-dione, and condensing first with 5-chloro-1*H*-indole-3-carbaldehyde, followed by 2-amino-5-methyl-1,3-thiazole-4-carbaldehyde. Mass: 498.19 (M+H).

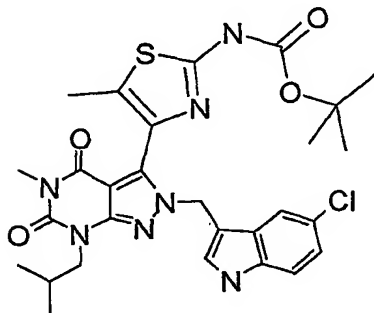
20

- 101 -

Example 119

tert-butyl 4-{2-[(5-chloro-1H-indol-3-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl}-5-methyl-1,3-thiazol-2-ylcarbamate

5

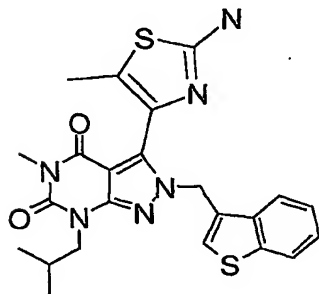


This compound was made following the procedure described above, starting with 6-hydrazino-1-isobutylpyrimidine-2,4(1*H*,3*H*)-dione, and condensing first with 5-chloro-1*H*-indole-3-carbaldehyde, followed by *tert*-butyl 4-formyl-5-methyl-1,3-thiazol-2-ylcarbamate. Mass: 598.22 (M+H).

15

Example 120

3-(2-amino-5-methyl-1,3-thiazol-4-yl)-2-(1-benzothien-3-ylmethyl)-7-isobutyl-5-methyl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5*H*,7*H*)-dione



20

- 102 -

(a) *tert*-butyl 4-[2-(1-benzothien-3-ylmethyl)-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-5-methyl-1,3-thiazol-2-ylcarbamate

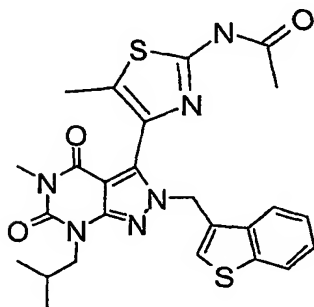
This compound was made following the procedure described above, starting with 6-hydrazino-1-isobutyl-3-methylpyrimidine-2,4(1*H*,3*H*)-dione, and condensing first with 1-benzothiophene-3-carbaldehyde, followed by *tert*-butyl 4-formyl-5-methyl-1,3-thiazol-2-ylcarbamate.

(b) 3-(2-amino-5-methyl-1,3-thiazol-4-yl)-2-(1-benzothien-3-ylmethyl)-7-isobutyl-5-methyl-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione

This compound was synthesized by treating *tert*-butyl 4-[2-(1-benzothien-3-ylmethyl)-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-5-methyl-1,3-thiazol-2-ylcarbamate with 4*M* HCl in dioxane at room temperature for 2.5 hours. Mass: 481.15 (M+H).

Example 121

N-{4-[2-(1-benzothien-3-ylmethyl)-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-5-methyl-1,3-thiazol-2-yl}acetamide



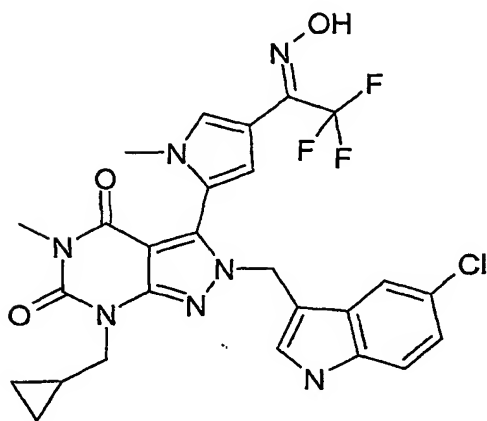
20

3-(2-amino-5-methyl-1,3-thiazol-4-yl)-2-(1-benzothien-3-ylmethyl)-7-isobutyl-5-methyl-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione hydrochloride was reacted with excess acetyl chloride using triethylamine as a base. The resulting bis acetylated product is treated with potassium carbonate to give the title compound. Mass: 523.22 (M+H).

25

Example 122

2-[(5-chloro-1*H*-indol-3-yl)methyl]-7-(cyclopropylmethyl)-5-methyl-3-{1-methyl-4-[(1*Z*)-
2,2,2-trifluoro-*N*-hydroxyethanimidoyl]-1*H*-pyrrol-2-yl}-2*H*-pyrazolo[3,4-*d*]pyrimidine-
5 4,6(5*H*,7*H*)-dione



Hydroxylamine hydrochloride (0.062 g) was added to a solution of 2-[(5-chloro-1*H*-indol-3-
10 yl)methyl]-7-(cyclopropylmethyl)-5-methyl-3-[1-methyl-4-(trifluoroacetyl)-1*H*-pyrrol-2-yl]-
2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (0.05 g) and triethylamine (0.063 ml) in
dimethylacetamide (5 ml) and the mixture heated at 80°C for 2 hours. Additional
hydroxylamine hydrochloride (0.062 g) was added and the reaction continued at 80°C for
another 3 hours. Cooled, concentrated, and the crude residue purified on preparative HPLC to
15 give the title compound (0.015 g). Mass: 574.17 (M+H).

Synthesis of some common intermediates used in the above reaction

sequence: methyl 5-formyl-1-methyl-1*H*-pyrrole-3-carboxylate Oxalylchloride (4.8
ml) in dichloroethane (10 ml) was added to a solution of dimethylformamide (4.25 ml) in
20 dichloroethane (20 ml) over a period of 20 minutes at ice-cold temperature. The white
suspension formed was stirred at room temperature for 20 minutes. Reaction cooled with ice-
cold water and *N*-methyl pyrrole (4.44 ml) in dichloroethane (10 ml) was added dropwise
over a period of 20 minutes. Resulting light yellow solution stirred at room temperature for 40
minutes. Aluminum chloride (13.33 g), followed by trichloroacetyl chloride (5.58 ml) was
25 added rapidly and the resulting dark mixture stirred at room temperature for 2 hours.

- 104 -

Methanol (70 ml) was added and stirred for 5 minutes. Sodium (5.6 g) dissolved in 70 ml methanol was added (external cooling was applied during the addition) and stirred at room temperature for one hour. Reaction mixture poured in to ice cold water, acidified with concentrated hydrochloric acid, and extracted with ether. Ether layer dried over sodium sulfate and concentrated. The residue treated with 100 ml of 0.5M sodium methoxide in methanol for 30 minutes. Then acidified with concentrated hydrochloric acid and extracted with ethyl acetate. Organic layer was dried and concentrated. The crude product was triturated with ether. Off white solid precipitated was filtered, washed with ether, and dried to give desired product (4.0 g).

10 .

5-formyl-1-methyl-1H-pyrrole-3-carboxylic acid

methyl 5-formyl-1-methyl-1H-pyrrole-3-carboxylate (0.5 g) dissolved in methanol (5 ml) was treated with 10% aqueous sodium hydroxide (5 ml) at 50°C for 2 hours. Reaction cooled, acidified with 10% aqueous hydrochloric acid, and extracted with ethyl acetate. Ethyl acetate layer dried, and concentrated to give pure desired acid (0.4 g).

15

1-methyl-4-(trifluoroacetyl)-1H-pyrrole-2-carbaldehyde

Oxalylchloride (4.8 ml) in dichloroethane (10 ml) was added to a solution of dimethylformamide (4.25 ml) in dichloroethane (20 ml) over a period of 20 minutes at ice-cold temperature. The white suspension formed was stirred at room temperature for 20 minutes. Reaction cooled with ice-cold water and N-methyl pyrrole (4.44 ml) in dichloroethane (10 ml) was added dropwise over a period of 20 minutes. Resulting light yellow solution stirred at room temperature for 40 minutes. Aluminum chloride (13.33 g), followed by trifluoroacetic anhydride (7 ml) was added rapidly and the resulting dark mixture stirred at room temperature for 2 hours. Reaction quenched with the addition of 100 ml 10% aqueous hydrochloric acid and extracted with ethyl acetate. Ethyl acetate layer dried, and concentrated. Crude product purified on column chromatography (silica-gel). Elution with 10-20% ethyl acetate in hexanes gave the desired product (0.1 g).

20

25

30 Substituted indole-3-carbaldehydes

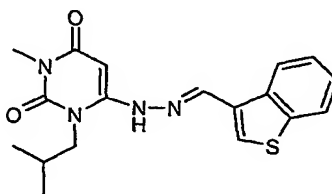
Substituted indole -3-carbaldehydes used in the synthesis are either purchased from the commercial sources or synthesized from the corresponding indoles using Vilsmeier reaction by following the procedure described in "Organic Functional Group Preparations" Second

- 105 -

Edition, Volume I, page 194, Academic Press, Inc. 1983, written by Stanley R. Sandler and Wolf Karo.

5 **Example 123**

Preparation of 1-benzothiophene-3-carbaldehyde N-(3-isobutyl-1-methyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinyl)hydrazone



10

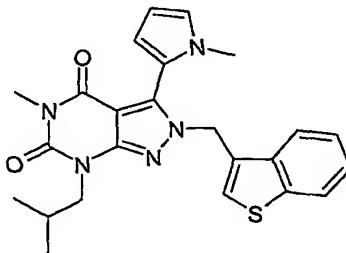
6-Hydrazino-1-isobutyl-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione (1.2 g, 5.65 mmol) was dissolved in methanol (100 mL). To the yellow/brown solution was added thianaphthene-3-carboxaldehyde (917 mg, 5.65 mmol). A brown precipitate began to form after about 20 min. The mixture was stirred at room temperature for 3 h under nitrogen gas. HPLC showed complete formation of hydrazone (Rt = 1.87 min, Kromasil, C8) The solvent was removed *in vacuo* and the brown slurry was pumped down to reveal a brown/yellow powder. Yield = 1.85 g (92%), TLC, Rf = 0.14 (CHCl₃/MeOH); Rt:1.87 min. MS:357 (M+H)

15

Example 124.

20

Preparation of 2-(1-benzothiophen-3-ylmethyl)-7-isobutyl-5-methyl-3-(1-methyl-1*H*-pyrrol-2-yl)-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione



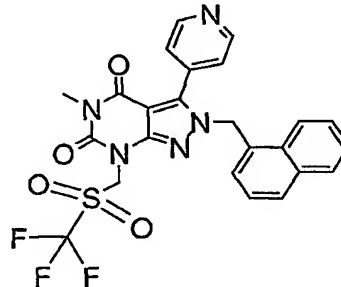
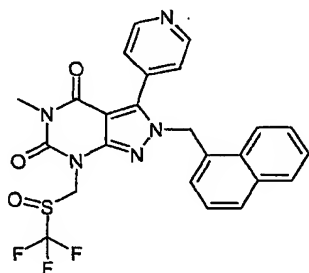
- 106 -

1-Benzothiophene-3-carbaldehyde N-(3-isobutyl-1-methyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinyl)hydrazone (100 mg, 0.284 mmol) was suspended in anh. DMA (3 mL) under an atmosphere of N₂ gas. To the suspension was added N-methylpyrrole-2-carboxaldehyde (37 mg, 0.34 mmol). To this suspension was added catalytic amounts of triethylamine (25 μ L). The reaction mixture was placed in a preheated heating block maintained at 90 °C and heated under N₂ gas for 18 h. At the end of reaction the solvent was removed in vacuo and the resulting brown oil was resuspended in DMSO (1.5 mL) and was purified by semi preparative RPHPLC eluting with MeCN/water/TFA mixtures. Yield = 37 mg, Rt= 2.46 min, MS: 444,(M+H).

10

Examples 125 and 126

(\pm)5-methyl-2-(1-naphthylmethyl)-3-(4-pyridinyl)-7-[[[(trifluoromethyl)sulfinyl]methyl]-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,7H)-dione and 5-methyl-2-(1-naphthylmethyl)-3-(4-pyridinyl)-7-[[[(trifluoromethyl)sulfonyl]methyl]-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione



A solution of 38 mg (0.73 mmol) of 5-methyl-2-(1-naphthylmethyl)-3-(4-pyridinyl)-7-[[[(trifluoromethyl)sulfonyl]methyl]-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione (Example 123) and 15 mg (0.73 mmol) of *m*-chloroperbenzoic acid in 1 mL CH₂Cl₂ was agitated at ambient temperature for 4 h. Solvent was removed and the residue was purified by HPLC (40%-80% gradient of CH₃CN-water with 0.1% TFA) to afford two materials as white solids as the trifluoroacetate salts. The longer retention time material was identified as the title sulfoxide and the shorter retention time material as the title sulfone.

25

MP 65-67 °C

LC-MS: RT = 2.31 min, ES⁺ (M+H) 529.7.LGDH I50: 18 μ M

- 107 -

MP 99-103°C

LC-MS: RT = 2.52 min, ES⁺ (M+H) 513.75.

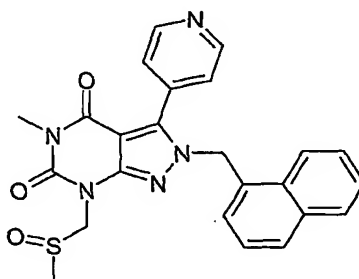
LGDH I50: 45.7 uM

5

Example 127

(±)5-methyl-7-[(methylsulfinyl)methyl]-2-(1-naphthylmethyl)-3-pyridin-4-yl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione

10



A solution of 40 mg (0.086 mmol) of 5-methyl-7-[(methylthio)methyl]-2-(1-naphthylmethyl)-3-pyridin-4-yl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione

7-isobutyl-5-methyl-2-(1-naphthylmethyl)-3-[3-(1H-1,2,3,4-tetraazol-5-yl)phenyl]-2H-

15 pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione (Example 124) in 2 mL MeOH and a solution of 19 mg (0.089 mmol) of NaIO₄ in 0.5 mL water were mixed together and agitated at ambient temperature for 3 d. The mixture was diluted with EtOAc which was washed with water and brine. Drying (MgSO₄) and removal of solvent gave 35 mg of the title material as a white solid.

20 MP 107-109 °C

LC-MS: RT = 1.98 min, ES⁺ (M+H) 459.84.

LGDH I50: 26 uM

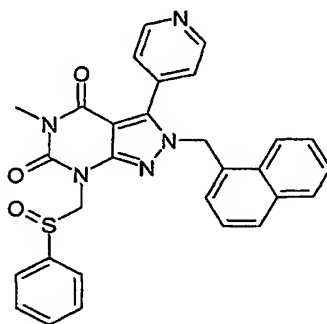
The following compound was made from 5-methyl-2-(1-naphthylmethyl)-7-[(phenylthio)methyl]-3-pyridin-4-yl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione

25 following the method described above.

Example 128

- 108 -

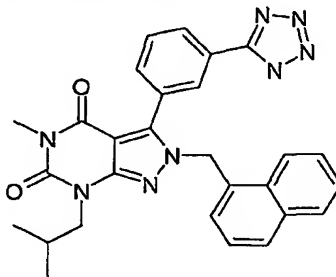
5-methyl-2-(1-naphthylmethyl)-7-[(phenylsulfinyl)methyl]-3-pyridin-4-yl-2H-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione



5 MP 130-135°C
LC-MS: RT = 2.37 min, ES⁺ (M+H) 521.79.

Example 129

7-isobutyl-5-methyl-2-(1-naphthylmethyl)-3-[3-(1*H*-1,2,3,4-tetraazol-5-yl)phenyl]-2H-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione



a) 3-[7-isobutyl-5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-*d*]pyrimidin-3-yl]benzonitrile

15

A solution of 100 mg (0.26 mmol) of 1-naphthaldehyde (3-isobutyl-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)hydrazone, 36 mg (0.27 mmol) of 3-cyano benzaldehyde and 20 uL of triethylamine in 20 mL DMF was heated at 85°C for 20 h. The mixture was diluted with ether and washed 4 times with water. The ether was dried (MgSO₄) and concentrated to give a yellow solid which was recrystallized from ethanol to give 84 mg of the subtitle product.

20

- 109 -

b) 7-isobutyl-5-methyl-2-(1-naphthylmethyl)-3-[3-(1*H*-1,2,3,4-tetraazol-5-yl)phenyl]-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione.

A solution of 84 mg (0.19 mmol) of the preceding product and 43 mg (0.21 mmol) of trimethyltin azide in 20 mL toluene was heated at reflux for 16 h. TLC (ether) showed the
 5 presence of starting material and a much more polar material. Additional trimethyltin azide (0.43 mg) was added, and the mixture was heated at reflux for 20 h. Starting material was still present by TLC, and 0.43 mg of trimethyltin azide was added. After heating at reflux 24 h, solvent was removed, and the residue was dissolved in 10 mL methanol. A solution of 3*N* HCl (5 mL) was added, and the mixture was stirred 60 min at ambient temperature. The
 10 mixture was partitioned between EtOAc and water. The organic layer was washed with brine, dried (MgSO₄) and concentrated to give an oil. The title product (13 mg) was isolated by HPLC (40%-80% gradient of CH₃CN-water with 0.1% TFA) as a white solid.

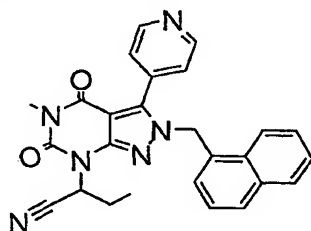
MP 251-254 °C

LC-MS: RT = 2.83 min, APCI⁺ (M+H) 506.85.

15 LGDH I50: 1.6 uM

Example 130

± 2-[5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-3-(4-pyridinyl)-2,4,5,6-tetrahydro-7*H*-
 20 pyrazolo[3,4-*d*]pyrimidin-7-yl]butanenitrile



A solution of 100 mg (0.26 mmol) of 5-methyl-2-(1-naphthylmethyl)-3-pyridin-4-yl-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione in 5 mL DMF was cooled in ice water
 25 before 280 µL (0.28 mmol) of 1 *N* potassium *t*-butoxide in THF was added. A solution of 51 mg (0.31 mmol) of 1-cyanopropyl methanesulfonate (Marco, J. L.; Ingate, S. T.; Jaime, C.; Bea, I. *Tetrahedron* **2000** *56*(16), 2523) in 1 mL DMF was added via syringe, and the mixture was heated at 80 °C overnight. Solvent was removed, and the residue was partitioned between EtOAc and water. The organic layer was washed twice more with water and once with brine

- 110 -

before being concentrated to give an oil. Purification by HPLC (40%-80% gradient of CH₃CN-water with 0.1% TFA) afforded the title product as a white solid as the trifluoroacetate salt.

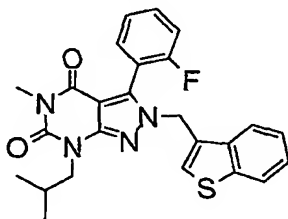
MP 75-77 °C

5 LC-MS: RT = 2.52 min, ES⁺ (M+H) 450.91.

LGDH I50: 9.1 uM

Example 131

10 **2-(1-benzothiophen-3-ylmethyl)-3-(2-fluorophenyl)-7-isobutyl-5-methyl-2H-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione**

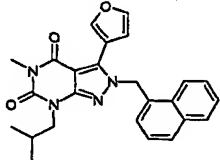
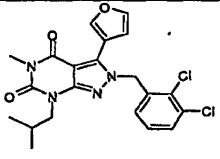
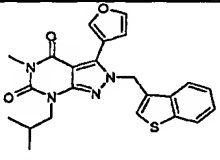
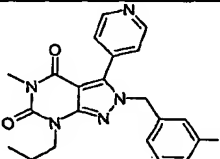
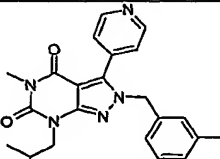


A solution of 100 mg (0.47 mmol) of 6-hydrazino-1-isobutyl-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione (Example 1d) and 76.4 mg (0.47 mmol) of 1-benzothiophene-3-carbaldehyde in 5 mL DMF was stirred at ambient temperature for 3 h. Added via syringe was 100 μL (0.95 mmol) of 2-fluorobenzaldehyde and 48 μL (0.48 mmol) of piperidine. The mixture was heated at 85 °C for 20 h. Solvent was removed, and the residue was purified by HPLC (60% CH₃CN-water with 0.1% TFA) to afford the title product as a white solid.

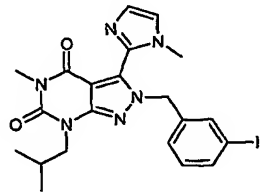
20 MP 55-57 °C

LC-MS: RT = 3.63 min, APCI⁺ (M+H) 463.2.

The following compounds were made from 6-hydrazino-1-isobutyl-3-methyl-2,4(1*H*,3*H*)-pyrimidine-dione (123d) and the appropriate carboxaldehyde following the method of procedure described above.

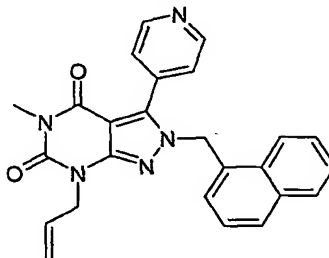
Example	Name	Mp (°C)	ES ⁺ (M+H)
 132	3-(3-furyl)-7-isobutyl-5-methyl-2-(1-naphthylmethyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione	151-154	428.88
 133	2-(2,3-dichlorobenzyl)-3-(3-furyl)-7-isobutyl-5-methyl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione	160-161	446.77, 448.78
 134	2-(1-benzothien-3-ylmethyl)-3-(3-furyl)-7-isobutyl-5-methyl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione	126-128	434.84
 135	2-(3-bromobenzyl)-7-isobutyl-5-methyl-3-pyridin-4-yl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione	165-166	467.78
 136	3-[(7-isobutyl-5-methyl-4,6-dioxo-3-pyridin-4-yl-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-2-yl)methyl]benzonitrile	188-192	414.89

- 112 -

Example	Name	Mp (°C)	ES ⁺ (M+H)
 137	2-(3-iodobenzyl)-7-isobutyl-5-methyl-3-(1-methyl-1 <i>H</i> -imidazol-2-yl)-2 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidine-4,6(5 <i>H</i> ,7 <i>H</i>)-dione	146-148	518.76

Example 138

Preparation of 7-allyl-5-methyl-2-(1-naphthylmethyl)-3-(4-pyridinyl)-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione



Allyl alcohol (17.7 μ L, 0.261 mmol) was dissolved in anh. CH₂Cl₂ (1 mL) and cooled to -5 °C. To this was added methanesulfonyl chloride (20.2 μ L, 0.261 mmol) followed by N,N'-diisopropylethylamine (45.4 μ L, 0.261 mmol). The mixture was stirred at low temperature for 2 h. Meanwhile, 5-methyl-2-(1-naphthylmethyl)-3-(4-pyridinyl)-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (100 mg, 0.261 mmol) was suspended in anh. N,N'-dimethylacetamide (2 mL) followed by addition of cesium carbonate (85 mg, 0.261 mmol). at room temperature for 1 h. To the mixture was added the preformed mesylate and the mixture was heated at 100 °C for 4 h. Reaction was partitioned between ethylacetate and water. The organic phase was washed with water, brine and dried over sodium sulfate and concentrated *in vacuo*. The crude product was purified by semi prep HPLC eluting with acetonitrile/water/TFA mixtures.

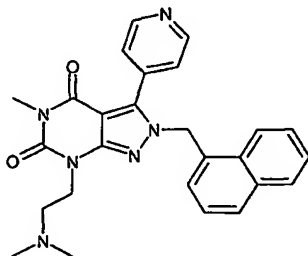
Yield : 57 mg; Rt =2.03 min; MS: 424(M+H).

- 113 -

Example 139

7-[2-(Dimethylamino)ethyl]-5-methyl-2-(1-naphthylmethyl)-3-(4-pyridinyl)-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione

5

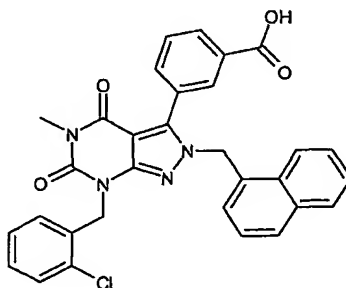


N-(2-Chloroethyl)-*N,N*-dimethylamine hydrochloride (0.058 g), followed by triethylamine (0.092 mL) and DBU (0.103 mL), were added to a solution of 5-methyl-2-(1-naphthylmethyl)-3-(4-pyridinyl)-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (0.064 g) in 3:1 dimethylformamide and DMSO (1 mL). The mixture was heated at 90 °C for 18 h then cooled to room temperature. Crude reaction was purified on preparative HPLC to give the title compound (0.120 g). Mass 455.03 (M+H).

Example 140

15

3-[7-(2-chlorobenzyl)-5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]benzoic acid



Diisopropylazodicarboxylate (0.157 g) was added to a mixture of resin bound 3-[5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]benzoic acid (0.120 g), triphenylphosphine (0.204 g), and 2-chlorophenylmethanol in dry THF (2 mL) at -15 °C. Reaction temperature was allowed to come to room temperature and

- 114 -

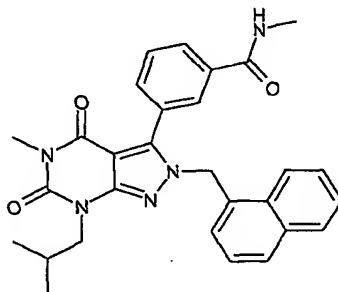
shaken for 20 h. The resin was filtered, washed (3 times) DMF, CH₂Cl₂, MeOH, CH₂Cl₂, and dried in vacuum. The dry resin was treated with 15% TFA in dichloromethane (1 mL) for 2 h, and filtered and washed (2 times) with dichloromethane. Combined filtrates were concentrated, and dried in vacuum to give the title compound (0.062 g). Mass 548.80 (M+H).

5

Example 141

3-[7-isobutyl-5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-*d*]pyrimidin-3-yl]-*N*-methylbenzamide

10

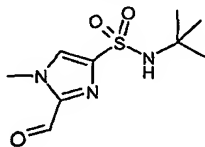


Triethylamine (0.04 mL) followed by isobutylchloroformate (0.033 g) were added to a solution of 3-[7-isobutyl-5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-*d*]pyrimidin-3-yl]benzoic acid (0.08 g) in THF (1 mL) at 0 °C. The mixture was stirred at 0 °C for 1 hour. Methylamine (2M, 2 mL) was added and the mixture was stirred at 0 °C for 1 h, then at room temperature for 2 h. Reaction was diluted with water (10 mL) and extracted with dichloromethane (2 X 10 mL). Combined organic layers were dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure. The residue was purified on preparative HPLC to give the title compound (0.027 g).

20

Example 142

Preparation of *N*-(*tert*-butyl)-2-formyl-1-methyl-1*H*-imidazole-4-sulfonamide



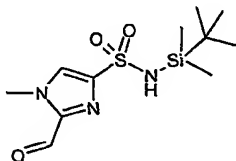
- 115 -

Step A) Preparation of *N*-(*tert*-butyl)-1-methyl-1*H*-imidazole-4-sulfonamide: A solution of 5.2 gm (29 mmol) 1-methyl-1*H*-imidazole-4-sulfonyl chloride in 30 mL THF was cooled in ice water while 7 mL *tert*-butylamine was added dropwise. The solution was warmed to room temperature and stirred overnight. Solids were filtered and rinsed with additional THF. The filtrate was concentrated to give a white solid that was recrystallized from water and dried in vacuo to give 4.8 gm of the subtitle compound, ¹H NMR (d6-DMSO) δ 7.75 (s, 1H), 7.65 (s, 1H), 7.2 (s, 1H), 3.7 (s, 3H), 1.1 (s, 9H).

Step B) A solution of 13 mL (21 mmol) of 1.6 M *n*-butyllithium in hexanes was added dropwise to a solution of 2.0 gm (9.2 mmol) the preceding product in 30 mL THF was cooled to -70°C. The mixture was warmed to room temperature and stirred 4 h before being cooled to -70°C. Dimethylformamide (0.8 mL, 10 mmol) was added all at once, and the solution was warmed to room temperature. The mixture was diluted with EtOAc and washed with water and brine. Drying (MgSO₄) and removal of solvent gave a solid that was purified by normal phase chromatography: 100% CH₂Cl₂ followed by gradient elution to 50% EtOAc in CH₂Cl₂. Two components were separated. The first eluting component was identified as the title compound, ¹H NMR (d6-DMSO) δ 9.8 (s, 1H), 8.0 (s, 1H), 7.6 (s, 1H), 4.0 (s, 3H), 1.2 (s, 9H).

Example 143

Preparation of *N*-[*tert*-butyl(dimethyl)silyl]-2-formyl-1-methyl-1*H*-imidazole-4-sulfonamide



Step A) Preparation of *N*-[*tert*-butyl(dimethyl)silyl]-1-methyl-1*H*-imidazole-4-sulfonamide: A mixture of 2.2 g (14 mmol) 1-methyl-1*H*-imidazole-4-sulfonamide, 2.1 g (14 mmol) *t*-butyldimethylsilyl chloride and 3.9 mL (28 mmol) triethylamine in 15 mL DMF was stirred at room temperature overnight. Solvent was removed, and the residue was dissolved in EtOAc before being washed with water and brine. Drying (MgSO₄) and removal of solvent gave 3 g

- 116 -

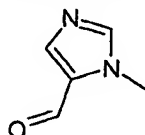
of the subtitle product as a white solid, ^1H NMR (DMSO) δ 7.7 (s, 1H), 7.6 (s, 1H), 7.35 (s, 1H), 3.7 (s, 3H), 0.9 (s, 9H), 0.2 (s, 6H).

Step B) A solution of 1.6 N *n*-butyllithium in hexanes (7.4 mL, 12 mmol) was added dropwise to a solution of 1.62 g (5.9 mmol) of the preceding product in 30 mL THF cooled to -70°C. The mixture was warmed to room temperature and stirred 2 h before being cooled to -70°C. Dimethylformamide (0.8 mL, 10 mmol) was added all at once, and the solution was warmed to room temperature. The mixture was diluted with EtOAc and washed with water and brine. Drying (MgSO_4) and removal of solvent gave a solid that was purified by normal phase chromatography: 100% CH_2Cl_2 followed by gradient elution to 30% EtOAc in CH_2Cl_2 . The first eluting component was identified as the title compound, ^1H NMR (d_6 -DMSO) δ 9.7 (s, 1H), 8.0 (s, 1H), 7.7 (s, 1H), 4.0 (s, 3H), 0.9 (s, 9H), 0.2 (s, 6H).

Example 144

15

Preparation of 1-methyl-1*H*-imidazole-5-carbaldehyde



Step A) Preparation of 4-(diethoxymethyl)-1*H*-imidazole: A mixture of 6.0 g (62.5 mmol) 1*H*-imidazole-4-carbaldehyde, 13 g (60 mmol) *p*-toluenesulfonic acid, 30 mL (180 mmol) triethylorthoformate and 6 g 4 Å molecular sieves in 100 mL EtOH was stirred at room temperature overnight. The mixture was filtered and rinsed through with EtOAc. Solvent was removed from the filtrate, and the residue was dissolved in EtOAc, washed with NaHCO_3 (aq), water and brine. Drying (MgSO_4) and removal of solvent gave 8 g of the subtitle product as a white solid, ^1H NMR (CDCl_3) δ 7.6 (s, 1H), 7.1 (s, 1H), 5.6 (s, 1H), 3.5-3.7 (m, 4H), 1.2 (m, 6H).

Step B) Preparation of 4-(diethoxymethyl)-1-trityl-1*H*-imidazole: A solution of 5.0 g (24 mmol) of the preceding product, 8.2 g (29.4 mmol) triphenylmethyl chloride and 4.1 mL (29 mmol) triethylamine in 200 mL THF was stirred at room temperature for 3 d. Solids were filtered, and the filtrate was diluted with Et_2O before being washed with water and brine.

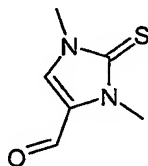
- 117 -

Drying (MgSO_4) and removal of solvent gave 6.2 g of the subtitle product as an oil, ^1H NMR (DMSO) δ 7.0-7.8 (m, 20H), 6.2 (s, 1H), 3.2-3.6 (m, 4H), 1.2 (m, 6H).

Step C) A solution of 6.2 g (15 mmol) of the preceding product and 10 g CH_3I in 200 mL
5 Et_2O was stirred at room temperature for 3 d. Solids were filtered and rinsed with additional Et_2O . The solids were taken up in 50% aqueous HOAc and stirred for 1 h. Solvent was removed, and the residue was dissolved in water before extraction with Et_2O . The aqueous phase was neutralized with NaHCO_3 and continuously extracted with EtOAc overnight. The EtOAc was dried (MgSO_4) and concentrated to give 1.0 g of the title product as a white solid,
10 ^1H NMR (DMSO) δ 9.8 (s, 1H), 8.2 (s, 1H), 7.9 (s, 1H), 3.9 (s, 3H).

Example 145

Preparation of 1,3-dimethyl-2-thioxo-2,3-dihydro-1H-imidazole-4-carbaldehyde

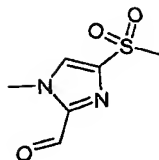


15 NaH (0.31 g, 13 mmol) was added to a solution of 2.0 g (12 mmol) 4-(diethoxymethyl)-1H-imidazole and 0.8 ml CH_3I in 30 mL DMF. Solvent was removed and the residue was dissolved in EtOAc and washed with water and brine. Drying (MgSO_4) and removal of solvent gave an oil that was dissolved in 50 mL THF along with 1 mL CH_3I . The solution was
20 heated at reflux for h. Solvent was removed and the residue was dissolved in 10 mL EtOH. Sulfur (0.11 g, 3.4 mmol) and K_2CO_3 (0.38 gm, 3.4 mmol) were added, and the mixture was heated at reflux for 2h. Solvent was removed and the residue was dissolved in 1:1 THF-1% aq HCl and stirred overnight. The mixture was partitioned between EtOAc and water. The organic layer was separated and washed with brine. Drying (MgSO_4) and removal of solvent
25 gave 250 mg of the title product as a yellow solid, ^1H NMR (CDCl_3) δ 9.4 (s, 1H), 7.7 (s, 1H), 7.5 (s, 1H), 3.9 (s, 3H), 3.7 (s, 3H).

Example 146

30 Preparation of 1-methyl-4-(methylsulfonyl)-1H-imidazole-2-carbaldehyde

- 118 -



Step A) Preparation of 2-(5,5-dimethyl-1,3-dioxan-2-yl)-1-methyl-1*H*-imidazole: A solution of 11.3 g (0.1 mol) 1-methyl-1*H*-imidazole-2-carbaldehyde, 11 g (0.11 mol) 2,2-dimethyl-1,3-propanediol and 21 g (0.11 mol) *p*-toluenesulfonic acid in 200 mL benzene was heated to
5 reflux with azeotropic removal of water for 3 h. After cooling to room temperature, the mixture was diluted with ether and washed with Na₂CO₃ (aq), water and brine. Drying (MgSO₄) and removal of solvent gave 18.7 g of an oil that slowly solidified, ¹H NMR (DMSO) δ 7.1 (s, 1H), 7.8 (s, 1H), 5.55 (s, 1H), 4.0 (s, 3H), 3.6 (ABq, 4H), 1.2 (s, 3H), 0.8 (s, 3H).

10

Step B) Preparation of 4,5-dibromo-2-(5,5-dimethyl-1,3-dioxan-2-yl)-1-methyl-1*H*-imidazole: A solution of 15.2 g (77.5 mmol) of the preceding product and 27.6 g (155 mmol) N-bromosuccinimide in 200 mL CHCl₃ was heated at reflux for 2 h. Insoluble solids were filtered and rinsed with CHCl₃, and solvent was removed from the filtrate. The residue was
15 dissolved in EtOAc, which was washed with 1N NaOH (aq), water and brine. Drying (MgSO₄) and removal of solvent gave 22 g of the subtitle compound as a solid, ¹H NMR (DMSO) δ 5.6 (s, 1H), 3.9 (s, 3H), 3.7 (ABq, 4H), 1.2 (s, 3H), 0.8 (s, 3H).

Step C) Preparation of 4-bromo-2-(5,5-dimethyl-1,3-dioxan-2-yl)-1-methyl-1*H*-imidazole: A
20 solution of 45 mL of 1.6 N *n*-butyllithium in hexanes (72 mmol) was added dropwise to a solution of 22 g (62 mmol) of the preceding compound in 200 mL THF cooled in a dry ice-acetone bath to maintain a temperature below -60°C. After stirring 5 m, the mixture was quenched with NaHCO₃ (aq) and warmed to room temperature. Dilution of the mixture with EtOAc was followed by washing with water and brine. Drying (MgSO₄) and removal of
25 solvent gave 16 g of a solid. Recrystallization from cyclohexane gave 11 g of the subtitle compound, ¹H NMR (DMSO) δ 7.3 (s, 1H), 5.5 (s, 1H), 3.8 (s, 3H), 3.7 (ABq, 4H), 1.4 (s, 3H), 0.8 (s, 3H).

Step D) Preparation of 2-(5,5-dimethyl-1,3-dioxan-2-yl)-1-methyl-4-(methylthio)-1*H*-
30 imidazole: A solution of 5.2 mL of 1.6 N *n*-butyllithium in hexanes (8.3 mmol) was added

- 119 -

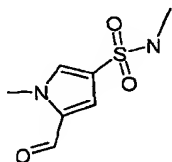
dropwise to a solution of 1.6 g (6.2 mmol) of the preceding compound in 200 mL THF cooled in a dry ice-acetone bath to maintain a temperature below -60°C . After stirring 5 m, (methyldithio)methane (750 μL , 8.3 mmol) was added in one portion, and the mixture was warmed to room temperature. Dilution with EtOAc was followed by washing with water and brine. Drying (MgSO_4) and removal of solvent gave a solid that was recrystallized from cyclohexane to give 390 mg of the subtitle compound, ^1H NMR (DMSO) δ 7.2 (s, 1H), 5.6 (s, 1H), 3.8 (s, 3H), 3.6 (ABq, 4H), 2.3 (s, 3H), 1.4 (s, 3H), 0.8 (s, 3H).

Step E) Preparation of 2-(5,5-dimethyl-1,3-dioxan-2-yl)-1-methyl-4-(methylsulfonyl)-1H-imidazole: A solution of 0.39 g (1.6 mmol) of the preceding compound and 0.8 g (3.3 mmol) of 70% *m*-chloroperoxybenzoic acid in 10 mL CH_2Cl_2 was stirred at room temperature for 2 h. The mixture was diluted with EtOAc and washed with NaHSO_3 (aq), Na_2CO_3 (aq) and brine. Drying (MgSO_4) and removal of solvent gave 0.44 g of the subtitle compound as a white solid, ^1H NMR (DMSO) δ 8.0 (s, 1H), 5.65 (s, 1H), 4.2 (s, 3H), 3.7 (ABq, 4H), 3.1 (s, 3H), 1.2 (s, 3H), 0.8 (s, 3H).

Step F) A solution of 0.44 g of the preceding compound in 30 mL of 2:1 THF-3N HCl was heated at reflux overnight. The mixture was basified with Na_2CO_3 (aq) and continuously extracted with EtOAc overnight. The EtOAc was dried (MgSO_4) and concentrated to give an oily solid. Trituration with Et_2O gave 170 mg of the title compound as a white solid, ^1H NMR (DMSO) δ 9.8 (s, 1H), 8.3 (s, 1H), 4.0 (s, 3H), 3.2 (s, 3H).

Example 147

25 Preparation of 5-formyl-*N*,1-dimethyl-1H-pyrrole-3-sulfonamide



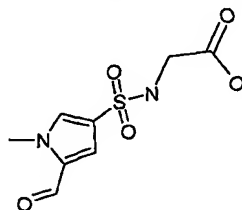
A solution of 0.8 g (3.3 mmol) *N*-(*tert*-butyl)-5-formyl-1-methyl-1H-pyrrole-3-sulfonamide, 1.2 g (9.8 mmol) K_2CO_3 and 1 mL (16 mmol) CH_3I in CH_3CN was heated at 60°C overnight. Solvent was removed, and the residue was partitioned between EtOAc and water. The organic layer was separated and washed with brine. Drying (MgSO_4) and removal of solvent to give

- 120 -

material that slowly solidified. The material was dissolved in 2 mL 1:1 CH₂Cl₂-TFA with stirring for 3 h. Solvent was removed to give the title compound as a solid, ¹H NMR (DMSO) δ 9.8 (s, 1H), 7.9 (s, 1H), 7.45 (s, 1H), 7.4 (s, 1H), 4.1 (s, 3H), 2.6 (s, 3H).

5 Example 148

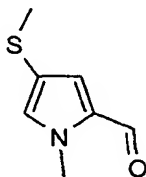
Preparation of *N*-[(5-formyl-1-methyl-1*H*-pyrrol-3-yl)sulfonyl]glycine



A solution of 0.8 g (3.3 mmol) *N*-(*tert*-butyl)-5-formyl-1-methyl-1*H*-pyrrole-3-sulfonamide, 10 1.2 g (9.8 mmol) K₂CO₃ and 1.4 g (7.2 mmol) *tert*-butyl bromoacetate in CH₃CN was heated at reflux overnight. Solvent was removed, and the residue was partitioned between EtOAc and water. The organic layer was separated and washed with brine. Drying (MgSO₄) and removal of solvent gave an oil that was chromatographed by normal phase (100% CH₂Cl₂ followed by gradient elution to 20 EtOAc in CH₂Cl₂) to give material that was dissolved in 2 mL 1:1 15 CH₂Cl₂-TFA with stirring overnight. Solvent was removed to give the title compound as a solid, ¹H NMR (DMSO) δ 9.6 (s, 1H), 7.4 (s, 1H), 7.2 (s, 1H), 4.1 (s, 3H), 3.9 (s, 2H).

Example 149

20 Preparation of 1-methyl-4-(methylthio)-1*H*-pyrrole-2-carbaldehyde



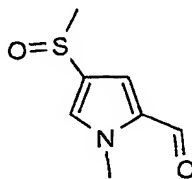
A solution of 22 mL of 1.6 N *n*-butyllithium (57 mmol) was added dropwise to a solution of 25 9.9 g (25 mmol) 2,7-dibromo-*N,N,N',N'*-tetramethyl-5*H*,10*H*-dipyrrolo[1,2-*a*:1',2'-*d*]pyrazine-5,10-diamine (Muchowski, J. M.; Hess, P. *Tetrahedron Lett.* **1988**, 29 (26), 3215-3218)

- 121 -

cooled in a dry ice acetone bath. The solution was stirred 10 m before 5 mL (57 mmol) of (methyldithio)methane was added in one portion. After warming to room temperature and stirring 2 h, 120 mL of NaHCO₃ (aq) were added, and the mixture was heated at reflux for 15 h. The mixture was diluted with EtOAc and washed with water and brine. Drying (MgSO₄) and removal of solvent gave a 7.5 g of a solid. The solid was dissolved in 50 mL DMF along with 6.9 g (50 mmol) K₂CO₃ and 3.1 mL (50 mmol) CH₃I. The mixture was heated at 50°C overnight. Solvent was removed, and the residue was partitioned between EtOAc and water. The EtOAc was separated and washed with brine. Drying (MgSO₄) and removal of solvent gave an oil that was used further without purification, ¹H NMR (DMSO) δ 9.5 (s, 1H), 7.3 (s, 1H), 7.0 (s, 1H), 3.9 (s, 3H), 2.4 (s, 3H).

Example 150

Preparation of 1-methyl-4-(methylsulfinyl)-1H-pyrrole-2-carbaldehyde

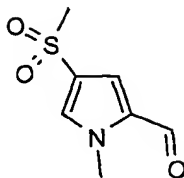


A solution of the preceding compound (0.54 g, 3.5 mmol) was dissolved in 20 mL MeOH, and a solution of 0.8 g (3.7 mmol) of NaIO₄ in 4 mL water was added. The mixture was stirred at room temperature overnight. MeOH was removed, and the residue was diluted with water before being extracted continuously with EtOAc overnight. The EtOAc was dried (MgSO₄) and concentrated to give the title compound, ¹H NMR (DMSO) δ 9.6 (s, 1H), 7.8 (s, 1H), 7.4 (s, 1H), 3.9 (s, 3H), 2.8 (s, 3H).

Example 151

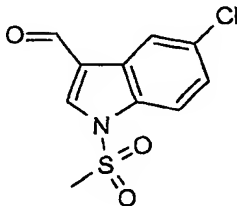
Preparation of 1-methyl-4-(methylsulfonyl)-1H-pyrrole-2-carbaldehyde

- 122 -



A solution of 1.0 g (6.4 mmol) 1-methyl-4-(methylthio)-1*H*-pyrrole-2-carbaldehyde and 3.1 g (13.3 mmol) *m*-chloroperoxybenzoic acid in 10 mL 1:1 CH₂Cl₂-H₂O (saturated with NaHCO₃) was stirred at room temperature for 2 h. The mixture was diluted with EtOAc and washed with NaHSO₃ (aq), NaHCO₃ (aq), and brine before being dried (MgSO₄) and concentrated. The resultant solid residue was recrystallized from *n*-butylchloride to give the title compound as a white solid, ¹H NMR (DMSO) δ 9.6 (s, 1H), 7.9 (s, 1H), 7.4 (s, 1H), 4.0 (s, 3H), 3.2 (s, 3H).

10

Example 152**Preparation of 5-chloro-1-(methanesulfonyl)-1*H*-indole-3-carbaldehyde**

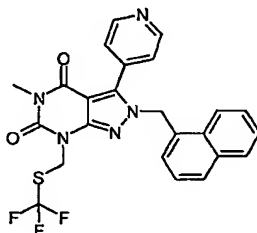
NaH (0.36 gm, 12.6 mmol) was added to a solution of 2.26 gm (12.6 mmol) 5-chloro-1*H*-indole-3-carbaldehyde in THF cooled in an ice water bath. After 20 m stirring, 1.4 g (12.6 mmol) methanesulfonyl chloride was added, and the solution was warmed to room temperature with stirring overnight. The mixture was diluted with EtOAc and washed with water and brine, dried (MgSO₄) and concentrated. Normal phase chromatography (CH₂Cl₂ followed by gradient elution to 10% EtOAc in CH₂Cl₂) afforded 1.9 gm of the title compound as a white solid, ¹H NMR (DMSO) δ 9.75 (s, 1H), 8.0 (s, 1H), 7.9 (s, 1H), 7.5 (d, 1H), 7.1 (d, 1H), 2.3 (s, 3H).

The preparations of 5-chloro-1-benzothiophene-3-carbaldehyde and 5-fluoro-1-benzothiophene-3-carbaldehyde are described in the literature (Branbender, H.J. *J.Heterocycl.Chem.* 1973, 10, 127).

25

Example 153 (old 160)

**5-methyl-2-(1-naphthylmethyl)-3-(4-pyridinyl)-7-[[trifluoromethyl]sulfanyl]methyl]-
 5 2H-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione**



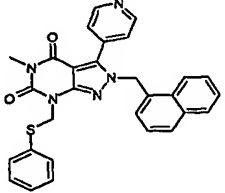
A solution of 150 mg (0.36 mmol) 5-methyl-2-(1-naphthylmethyl)-3-pyridin-4-yl-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione, 61 mg (0.47 mmol) K₂CO₃ and 50 μL (0.47 mmol) chloromethyl trifluoromethylsulfide in 10 mL DMF was heated at 80°C for 20 h. The mixture was diluted with ether and washed 3 times with water. Drying (MgSO₄) and removal
 10 of solvent gave a yellow solid that was recrystallized from ethanol to give 95 mg of a white solid.

ES⁺ (M+H) 497.78.

15 Following the method of Example 153, Compounds 154 and 155 were made by reaction of 5-methyl-2-(1-naphthylmethyl)-3-pyridin-4-yl-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione with chloromethyl methylsulfide and chloromethyl phenyl sulfide, respectively,

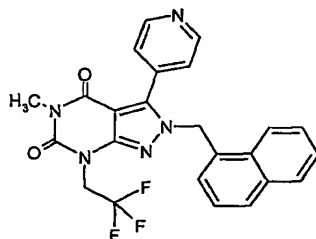
Example	Structure	Name	ES ⁺ (M+H)
154		5-methyl-7-[(methylthio)methyl]- 2-(1-naphthylmethyl)-3-pyridin-4- yl-2 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidine- 4,6(5 <i>H</i> ,7 <i>H</i>)-dione	443.94

- 124 -

155		5-methyl-2-(1-naphthylmethyl)-7-[(phenylthio)methyl]-3-pyridin-4-yl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione	505.82
-----	---	---	--------

Example 156

5-methyl-2-(1-naphthylmethyl)-3-pyridin-4-yl-7-(2,2,2-trifluoroethyl)-2H-pyrazolo[3,4-
5 d]pyrimidine-4,6(5H,7H)-dione



A solution of 84 mg (0.54 mmol) 6-hydrazino-3-methylpyrimidine-2,4(1H,3H)-dione and 84 mg (0.54 mmol) 1-naphthaldehyde in 3 mL DMF was heated to 70°C for 30 min before cooling to room temperature affording a solution of 1-naphthaldehyde (1-methyl-2,6-dioxo-
10 1,2,3,6-tetrahydropyrimidin-4-yl)hydrazone. Isonicotinaldehyde (110 mg, 1.0 mmol) and piperidine (50 µL, 0.6 mmol) were added, and the mixture was heated at 70°C for 20 h. 1,1,1-trifluoro-2-iodoethane (130 µL, 1.3 mmol) and DBU (200 µL, 1.3 mmol) were added, and the mixture was heated at 90°C for 20 h. Solvent was removed and the residue was purified by preparative reverse phase HPLC (30%-60% gradient of CH₃CN-water with 0.1% TFA) to
15 afford the title compound as the trifluoroacetate salt.

ES⁺ (M+H) 466.38.

Following the method of Example 156, Compound 157 was made by preparation of 1-naphthaldehyde (1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)hydrazone and
20 condensation with 1-methyl-1H-imidazole-2-carbaldehyde followed by alkylation with 1,1,1-trifluoro-2-iodoethane.

- 125 -

Following the method of Example 156, the compound of Example 158 was made by preparation of 1-naphthaldehyde (1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)hydrazone and condensation with isonicotinaldehyde followed by alkylation with 1-bromo-3-fluoropropane.

5

Following the method of Example 156, the compound of Example 159 was made by preparation of 1-benzothiophene-3-carbaldehyde (1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)hydrazone and condensation with 1-methyl-1*H*-imidazole-2-carbaldehyde followed by alkylation with 1-bromo-3-fluoropropane.

10

Following the method of Example 156, the compound of Example 160 was made by condensation of 1-benzothiophene-3-carbaldehyde (1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)hydrazone and condensation with 1-methyl-1*H*-imidazole-2-carbaldehyde followed by alkylation with *n*-propyl iodide.

15

Following the method of Example 156, the compound of Example 161 was made by preparation of 1-benzothiophene-3-carbaldehyde (1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)hydrazone and condensation with 1-methyl-1*H*-imidazole-2-carbaldehyde followed by alkylation with 1,1,1-trifluoro-2-iodoethane.

20

Following the method of Example 156, the compound of Example 162 was made by condensation of 1-benzothiophene-3-carbaldehyde (1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)hydrazone and condensation with isonicotinaldehyde followed by alkylation with 1,1,1-trifluoro-2-iodoethane.

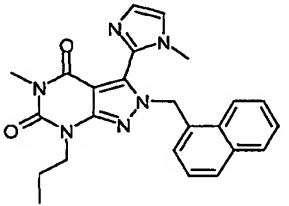
25

Following the method of Example 156, the compound of Example 163 was made by preparation of 1-naphthaldehyde (1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)hydrazone and condensation with 1-methyl-1*H*-imidazole-2-carbaldehyde followed by alkylation with *n*-propyl iodide.

30

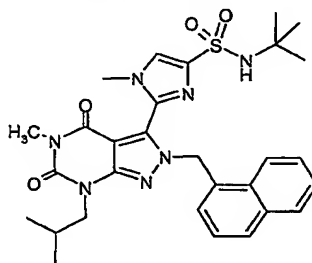
Example	Structure	Name	ES ⁺ (M+H)
157		5-methyl-3-(1-methyl-1 <i>H</i> -imidazol-2-yl)-2-(1-naphthylmethyl)-7-(2,2,2-trifluoroethyl)-2 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidine-4,6(5 <i>H</i> ,7 <i>H</i>)-dione	469.38
158		7-(3-fluoropropyl)-5-methyl-3-(1-methyl-1 <i>H</i> -imidazol-2-yl)-2-(1-naphthylmethyl)-2 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidine-4,6(5 <i>H</i> ,7 <i>H</i>)-dione	447.18
159		2-(1-benzothien-3-ylmethyl)-7-(3-fluoropropyl)-5-methyl-3-(1-methyl-1 <i>H</i> -imidazol-2-yl)-2 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidine-4,6(5 <i>H</i> ,7 <i>H</i>)-dione	453.20
160		2-(1-benzothien-3-ylmethyl)-5-methyl-3-(1-methyl-1 <i>H</i> -imidazol-2-yl)-7-propyl-2 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidine-4,6(5 <i>H</i> ,7 <i>H</i>)-dione	429.4
161		2-(1-benzothien-3-ylmethyl)-5-methyl-3-(1-methyl-1 <i>H</i> -imidazol-2-yl)-7-(2,2,2-trifluoroethyl)-2 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidine-4,6(5 <i>H</i> ,7 <i>H</i>)-dione	475.40
162		2-(1-benzothien-3-ylmethyl)-5-methyl-3-pyridin-4-yl-7-(2,2,2-trifluoroethyl)-2 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidine-4,6(5 <i>H</i> ,7 <i>H</i>)-dione	472.40

- 127 -

163		5-methyl-3-(1-methyl-1H-imidazol-2-yl)-2-(1-naphthalenylmethyl)-7-propyl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione	429.40
-----	---	--	--------

Example 164

- 5 ***N*-(*tert*-butyl)-2-[7-isobutyl-5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-1-methyl-1*H*-imidazole-4-sulfonamide**



- A solution of 190 mg (1.1 mmol) of 1-naphthaldehyde (3-isobutyl-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)hydrazone, 36 mg (0.27 mmol) of *N*-(*tert*-butyl)-2-formyl-1-methyl-1*H*-imidazole-4-sulfonamide and 40 μ L of piperidine in 3 mL DMF was heated at 70°C for 20 h. Solvent was removed, and the mixture was isolated by preparative reverse phase HPLC (60%-90% gradient of CH₃CN-water with 0.1% TFA) as a white solid.

ES⁺ (M+H) 578.17.

15

- Following the method of Example 164, the compound of Example 165 was made by condensation of 1-naphthaldehyde (3-isobutyl-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)hydrazone with *N*-(*tert*-butyl)-3-formylbenzenesulfonamide (Martin, L.; Cornille, F.; Turcaud, S.; Meudal, H.; Roques, B. P.; Fournie-Zaluski, M-C. *J. Med. Chem.* 42(3), 1999, 515-525).

20

Following the method of Example 164, the compound of Example 166 was made by condensation of 5-chloro-1*H*-indole-3-carbaldehyde (3-isobutyl-1-methyl-2,6-dioxo-1,2,3,6-

- 128 -

tetrahydropyrimidin-4-yl)hydrazone with *N*-(*tert*-butyl)-1-methyl-1*H*-imidazole-4-sulfonamide.

Following the method of Example 164, the compound of Example 167 was made by
5 condensation of 5-chloro-1*H*-indole-3-carbaldehyde (3-isobutyl-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)hydrazone with 1-methyl-1*H*-imidazole-5-carbaldehyde.

Following the method of Example 164, the compound of Example 168 was made by
condensation of 1-naphthaldehyde (3-isobutyl-1-methyl-2,6-dioxo-1,2,3,6-
10 tetrahydropyrimidin-4-yl)hydrazone with 1-methyl-1*H*-imidazole-5-carbaldehyde.

Following the method of Example 164, the compound of Example 169 was made by
condensation of 1-naphthaldehyde (3-isobutyl-1-methyl-2,6-dioxo-1,2,3,6-
tetrahydropyrimidin-4-yl)hydrazone with 1,3-dimethyl-2-thioxo-2,3-dihydro-1*H*-imidazole-4-
15 carbaldehyde.

Following the method of Example 164, the compound of Example 170 was made by
condensation of 5-fluoro-3a,7a-dihydro-1-benzothiophene-3-carbaldehyde (3-isobutyl-1-
methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)hydrazone with 3-
20 formylbenzenesulfonamide (Roussel-UCLAF, NL 6405788; 1964; Chem.Abstr.: 63, 9917b, 1965).

Following the method of Example 164, the compound of Example 171 was made by
condensation of 5-methyl-3a,7a-dihydro-1*H*-indole-3-carbaldehyde (3-isobutyl-1-methyl-2,6-
25 dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)hydrazone with 3-formylbenzenesulfonamide
(Roussel-UCLAF, NL 6405788; 1964; Chem.Abstr.: 63, 9917b, 1965).

Following the method of Example 164, the compound of Example 172 was made by
condensation of 5-methyl-3a,7a-dihydro-1*H*-indole-3-carbaldehyde (3-isobutyl-1-methyl-2,6-
30 dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)hydrazone with 3-formylbenzenesulfonamide
(Roussel-UCLAF, NL 6405788; 1964; Chem.Abstr.: 63, 9917b, 1965).

- 129 -

Following the method of Example 164, the compound of Example 173 was made by condensation of 5-fluoro-3a,7a-dihydro-1-benzothiophene-3-carbaldehyde (3-isobutyl-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)hydrazone with 1-methyl-1*H*-imidazole-5-carbaldehyde.

5

Following the method of Example 164, the compound of Example 174 was made by condensation of 5-methyl-3a,7a-dihydro-1*H*-indole-3-carbaldehyde (3-isobutyl-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)hydrazone with 1-methyl-1*H*-imidazole-5-carbaldehyde.

10

Following the method of Example 164, the compound of Example 175 was made by condensation of 1-benzothiophene-3-carbaldehyde (1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)hydrazone with 1-methyl-1*H*-imidazole-5-carbaldehyde.

15

Following the method of Example 164, the compound of Example 176 was made by condensation of 1-naphthaldehyde (3-isobutyl-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)hydrazone with 1,3-dimethyl-2-thioxo-2,3-dihydro-1*H*-imidazole-4-carbaldehyde.

20

Following the method of Example 164, the compound of Example 177 was made by condensation of 5-chloro-1*H*-indole-3-carbaldehyde (3-isobutyl-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)hydrazone with *N*-[*tert*-butyl(dimethyl)silyl]-2-formyl-1-methyl-1*H*-imidazole-4-sulfonamide.

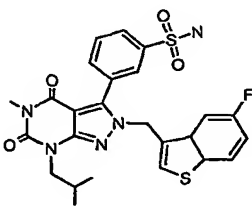
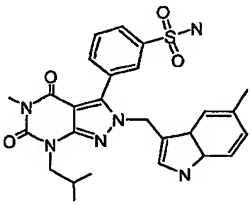
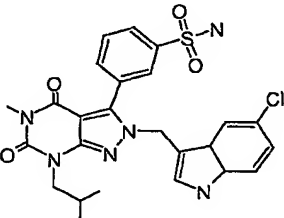
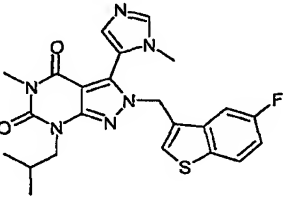
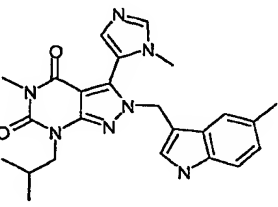
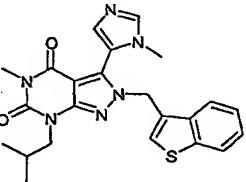
25

Following the method of Example 164, the compound of Example 178 was made by condensation of 5-chloro-1*H*-indole-3-carbaldehyde [3-(cyclopropylmethyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl]hydrazone with *N*-[*tert*-butyl(dimethyl)silyl]-2-formyl-1-methyl-1*H*-imidazole-4-sulfonamide.

30

Following the method of Example 164, the compound of Example 179 was made by condensation of 5-methyl-1*H*-indole-3-carbaldehyde [3-(cyclopropylmethyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl]hydrazone with *N*-[*tert*-butyl(dimethyl)silyl]-2-formyl-1-methyl-1*H*-imidazole-4-sulfonamide.

Example	Structure	Name	ES ⁺ (M+H)
165		<i>N</i> -(<i>tert</i> -butyl)-3-[7-isobutyl-5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl]benzenesulfonamide	574.18.
166		<i>N</i> -(<i>tert</i> -butyl)-2-{2-[(5-chloro-1 <i>H</i> -indol-3-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl}-1-methyl-1 <i>H</i> -imidazole-4-sulfonamide	601.09
167		2-[(5-chloro-1 <i>H</i> -indol-3-yl)methyl]-7-isobutyl-5-methyl-3-(1-methyl-1 <i>H</i> -imidazol-5-yl)-2 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidine-4,6(5 <i>H</i> ,7 <i>H</i>)-dione	466.14
168		7-isobutyl-5-methyl-3-(1-methyl-1 <i>H</i> -imidazol-5-yl)-2-(1-naphthylmethyl)-2 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidine-4,6(5 <i>H</i> ,7 <i>H</i>)-dione	443.22
169		2-[(5-chloro-1 <i>H</i> -indol-3-yl)methyl]-3-(1,3-dimethyl-2-thioxo-2,3-dihydro-1 <i>H</i> -imidazol-4-yl)-7-isobutyl-5-methyl-2 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidine-4,6(5 <i>H</i> ,7 <i>H</i>)-dione	512.17

170		3-{2-[(5-fluoro-3a,7a-dihydro-1-benzothien-3-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl}benzenesulfonamide	542.03
171		3-{7-isobutyl-5-methyl-2-[(5-methyl-3a,7a-dihydro-1H-indol-3-yl)methyl]-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl}benzenesulfonamide	521.08
172		3-{2-[(5-chloro-3a,7a-dihydro-1H-indol-3-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl}benzenesulfonamide	541.07
173		2-[(5-fluoro-1-benzothien-3-yl)methyl]-7-isobutyl-5-methyl-3-(1-methyl-1H-imidazol-5-yl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione	467.04
174		7-isobutyl-5-methyl-3-(1-methyl-1H-imidazol-5-yl)-2-[(5-methyl-1H-indol-3-yl)methyl]-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione	446.31
175		2-(1-benzothien-3-ylmethyl)-7-isobutyl-5-methyl-3-(1-methyl-1H-imidazol-5-yl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione	449.19

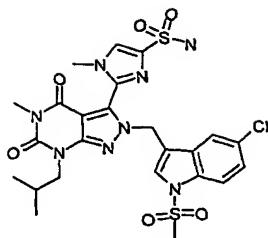
- 132 -

176		3-(1,3-dimethyl-2-thioxo-2,3-dihydro-1H-imidazol-4-yl)-7-isobutyl-5-methyl-2-(1-naphthylmethyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione	489.23
177		2-{2-[(5-chloro-1H-indol-3-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl}-1-methyl-1H-imidazole-4-sulfonamide	545.12
178		2-[2-[(5-chloro-1H-indol-3-yl)methyl]-7-(cyclopropylmethyl)-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]-1-methyl-1H-imidazole-4-sulfonamide	543.12
179		2-{7-(cyclopropylmethyl)-5-methyl-2-[(5-methyl-1H-indol-3-yl)methyl]-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl}-1-methyl-1H-imidazole-4-sulfonamide	523.15

Example 180

- 5 2-(2-{[5-chloro-1-(methylsulfonyl)-1H-indol-3-yl]methyl}-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl)-1-methyl-1H-imidazole-4-sulfonamide

- 133 -



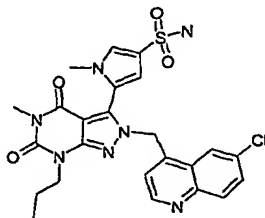
A solution of 38 mg (0.18 mmol) of 6-hydrazino-1-isobutyl-3-methylpyrimidine-2,4(1*H*,3*H*)-dione and 5-chloro-1-(methylsulfonyl)-1*H*-indole-3-carbaldehyde in 2 mL DMF was stirred at
 5 room temperature for 2 h. Added was 88 mg (0.36 mmol) *N*-(*tert*-butyl)-2-formyl-1-methyl-1*H*-imidazole-4-sulfonamide and 15 μ L piperidine. The solution was heated at 70°C for 20 h. Solvent was removed, and the residue was dissolved in 2 mL 1:1 CH₂Cl₂-TFA with stirring overnight. Solvent was removed, and the mixture was isolated by preparative reverse phase HPLC (30%-50% gradient of CH₃CN-water with 0.1% TFA) as a white solid.

10

ES⁺ (M+H) 622.48.

Example 181

15 5-{2-[(6-chloroquinolin-4-yl)methyl]-5-methyl-4,6-dioxo-7-propyl-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-1-methyl-1*H*-pyrrole-3-sulfonamide



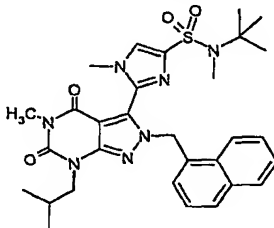
Following the method of Example 180, this compound was made by preparation of 6-chloroquinoline-4-carbaldehyde (1-methyl-2,6-dioxo-3-propyl-1,2,3,6-tetrahydropyrimidin-4-yl)hydrazone, condensation with *N*-(*tert*-butyl)-5-formyl-1-methyl-1*H*-pyrrole-3-sulfonamide
 20 and treatment with TFA.

ES⁺ (M+H) 542.12.

- 134 -

Example 182

N-(*tert*-butyl)-2-[7-isobutyl-5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-*N*,1-dimethyl-1*H*-imidazole-4-sulfonamide



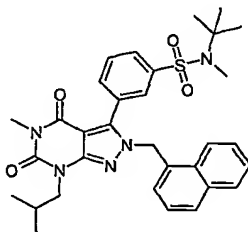
5

NaH (10 mg, 0.25 mmol) was added to a solution of the compound of Example 164 (84 mg, 0.14 mmol) and CH₃I (100 μ L) in 2 mL DMF. After warming to room temperature and stirring for 16 h, solvent was removed and the residue was partitioned between water and EtOAc. The EtOAc was separated and washed with brine. Drying and removal of solvent
10 gave an oil that was purified by preparative reverse phase HPLC (45%-75% gradient of CH₃CN-water with 0.1% TFA).

ES⁺ (M+H) 592.19.

15 **Example 183**

N-(*tert*-butyl)-3-[7-isobutyl-5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-*N*-methylbenzenesulfonamide



20

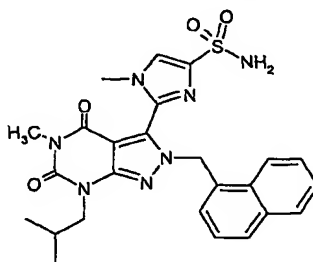
Following the method of Example 182, the title compound was made from the compound of Example 165.

25 ES⁺ (M+H) 588.20.

- 135 -

Example 184

2-[7-isobutyl-5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-
 5 pyrazolo[3,4-*d*]pyrimidin-3-yl]-1-methyl-1*H*-imidazole-4-sulfonamide



A solution of 200 mg (.37 mmol) of the compound made in Example 164 in 4 mL of 1:1
 CH₂Cl₂:TFA was stirred at room temperature overnight. Solvent was removed, and the
 residue was purified by preparative HPLC (30%-55% gradient of CH₃CN-water with 0.1%
 10 TFA) to give the title compound as a TFA salt.

ES⁺ (M+H) 522.08.

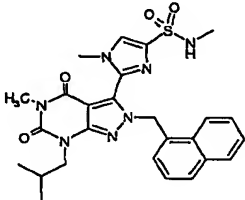
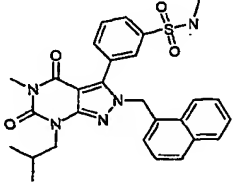
Following the method of Example 184, the compound of Example 185 was made from the
 15 compound of Example 165.

Following the method of Example 184, the compound of Example 186 was made from the
 compound from Example 182.

20 Following the method of Example 184, the compound of Example 187 was made from the
 from Example 183.

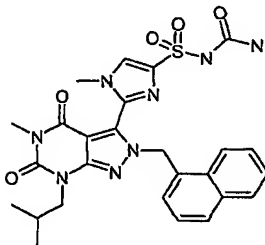
Example	Structure	Name	ES ⁺ (M+H)
185		3-[7-isobutyl-5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4- <i>d</i>]pyrimidin-3-	518.11

- 136 -

		yl]benzenesulfonamide	
186		2-[7-isobutyl-5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]-N,1-dimethyl-1H-imidazole-4-sulfonamide	536.13
187		3-[7-isobutyl-5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]-N-methylbenzenesulfonamide	532.13

Example 188

N-(aminocarbonyl)-2-[7-isobutyl-5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]-1-methyl-1H-imidazole-4-sulfonamide



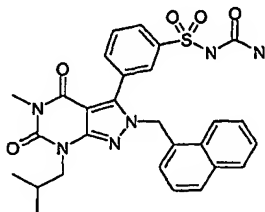
A solution of 44 mg (84 μ mol) of the compound of Example 184, 65 mg (0.48 mmol) phenyl carbamate and 66 μ L (0.48 mmol) DBU in 3 mL CH_3CN were stirred together at room temperature overnight. Solvent was removed and the residue was purified by preparative HPLC (30%-50% gradient of CH_3CN -water with 0.1% TFA) to give the title compound as the TFA salt.

ES^+ (M+H) 565.13.

Example 189

- 137 -

***N*-(aminocarbonyl)-3-[7-isobutyl-5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]benzenesulfonamide**



5

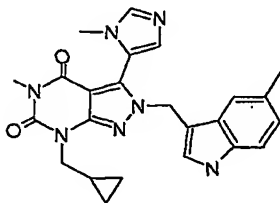
Following the method of Example 88, the title compound was made from the compound of Example 185.

ES⁺ (M+H) 561.26.

10

Example 190

7-(cyclopropylmethyl)-5-methyl-3-(1-methyl-1*H*-imidazol-5-yl)-2-[(5-methyl-1*H*-indol-3-yl)methyl]-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione



15

A solution of 90 mg (0.26 mmol) 5-methyl-1*H*-indole-3-carbaldehyde [3-(cyclopropylmethyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl]hydrazone, 39 mg (0.35 mmol) 1-methyl-1*H*-imidazole-5-carbaldehyde and 22 μ L piperidine in 1 mL DMF was heated at 110°C for 12 m via microwave irradiation. Purification was achieved by preparative HPLC (30%-50% gradient of CH₃CN-water with 0.1% TFA) to give the title compound as the TFA salt.

20

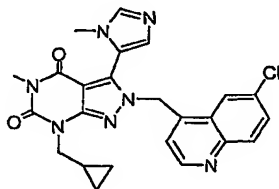
ES⁺ (M+H) 444.29.

Example 191

25

- 138 -

2-[(6-chloroquinolin-4-yl)methyl]-7-(cyclopropylmethyl)-5-methyl-3-(1-methyl-1*H*-imidazol-5-yl)-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione



- 5 A solution of 49 mg (0.23 mmol) 1-(cyclopropylmethyl)-6-hydrazino-3-methylpyrimidine-2,4(1*H*,3*H*)-dione and 44 mg (0.23 mmol) 6-chloroquinoline-4-carbaldehyde in 1 mL DMF was stirred at room temperature for 5 h to form 6-chloroquinoline-4-carbaldehyde [3-(cyclopropylmethyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl]hydrazone. Added was 38 mg (0.34 mmol) 1-methyl-1*H*-imidazole-5-carbaldehyde and 20 μ L piperidine. The
- 10 mixture was heated at 110°C for 12 via microwave irradiation. Purification was achieved by preparative HPLC (20%-40% gradient of CH₃CN-water with 0.1% TFA) to give the title compound as the bis-TFA salt.

ES⁺ (M+H) 476.21.

15

Following the method of Example 191, the compound of Example 192 was made by preparation of 6-chloroquinoline-4-carbaldehyde (3-isobutyl-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)hydrazone and condensation with 1-methyl-1*H*-imidazole-5-carbaldehyde.

20

Following the method of Example 191, the compound of Example 193 was made by preparation of 5-chloro-1*H*-indole-3-carbaldehyde (3-isobutyl-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)hydrazone and condensation with 1-methyl-1*H*-imidazole-5-carbaldehyde.

25

Following the method of Example 191, the compound of Example 194 was made by preparation of 5-chloro-1*H*-indole-3-carbaldehyde [3-(cyclopropylmethyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl]hydrazone and condensation with 1-methyl-1*H*-imidazole-5-carbaldehyde.

30

- 139 -

Following the method of Example 191, the compound of Example 195 was made by preparation of 6-chloroquinoline-4-carbaldehyde (3-isobutyl-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)hydrazone and condensation with *N*-[*tert*-butyl(dimethyl)silyl]-2-formyl-1-methyl-1*H*-imidazole-4-sulfonamide.

5

Following the method of Example 191, the compound of Example 196 was made by preparation of 6-chloroquinoline-4-carbaldehyde [3-(cyclopropylmethyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl]hydrazone and condensation with *N*-[*tert*-butyl(dimethyl)silyl]-2-formyl-1-methyl-1*H*-imidazole-4-sulfonamide.

10

Following the method of Example 191, the compound of Example 197 was made by preparation of 5-chloro-1*H*-indole-3-carbaldehyde (3-isobutyl-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)hydrazone and condensation with 1-methyl-4-(methylsulfonyl)-1*H*-imidazole-2-carbaldehyde.

15

Following the method of Example 191, the compound of Example 198 was made by preparation of 5-chloro-1*H*-indole-3-carbaldehyde [3-(cyclopropylmethyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl]hydrazone and condensation with 1-methyl-4-(methylsulfonyl)-1*H*-imidazole-2-carbaldehyde.

20

Following the method of Example 191, the compound of Example 199 was made by preparation of 6-chloroquinoline-4-carbaldehyde (1-methyl-2,6-dioxo-3-propyl-1,2,3,6-tetrahydropyrimidin-4-yl)hydrazone and condensation with 5-formyl-*N*,1-dimethyl-1*H*-pyrrole-3-sulfonamide.

25

Following the method of Example 191, the compound of Example 200 was made by preparation of 5-chloro-1*H*-indole-3-carbaldehyde [3-(cyclopropylmethyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl]hydrazone and condensation with 5-formyl-*N*,1-dimethyl-1*H*-pyrrole-3-sulfonamide.

30

Following the method of Example 191, the compound of Example 201 was made by preparation of 5-chloro-1*H*-indole-3-carbaldehyde (3-isobutyl-1-methyl-2,6-dioxo-1,2,3,6-

- 140 -

tetrahydropyrimidin-4-yl)hydrazone and condensation with 5-formyl-*N*,1-dimethyl-1*H*-pyrrole-3-sulfonamide.

Following the method of Example 191, the compound of Example 202 was made by
5 preparation of 5-methyl-1*H*-indole-3-carbaldehyde [3-(cyclopropylmethyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl]hydrazone and condensation with 5-formyl-*N*,1-dimethyl-1*H*-pyrrole-3-sulfonamide.

Following the method of Example 191, the compound of Example 203 was made by
10 preparation of 5-methyl-3*a*,7*a*-dihydro-1*H*-indole-3-carbaldehyde (3-isobutyl-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)hydrazone and condensation with 5-formyl-*N*,1-dimethyl-1*H*-pyrrole-3-sulfonamide.

Following the method of Example 191, the compound of Example 204 was made by
15 preparation of 6-chloroquinoline-4-carbaldehyde [3-(cyclopropylmethyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl]hydrazone and condensation with 5-formyl-*N*,1-dimethyl-1*H*-pyrrole-3-sulfonamide.

Following the method of Example 191, the compound of Example 205 was made by
20 preparation of 6-chloroquinoline-4-carbaldehyde (3-isobutyl-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)hydrazone and condensation with 5-formyl-*N*,1-dimethyl-1*H*-pyrrole-3-sulfonamide.

Following the method of Example 191, the compound of Example 206 was made by
25 preparation of 5-fluoro-1-benzothiophene-3-carbaldehyde [3-(cyclopropylmethyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl]hydrazone and condensation with 5-formyl-*N*,1-dimethyl-1*H*-pyrrole-3-sulfonamide.

Following the method of Example 191, the compound of Example 207 was made by
30 preparation of 5-fluoro-1-benzothiophene-3-carbaldehyde (3-isobutyl-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)hydrazone and condensation with 5-formyl-*N*,1-dimethyl-1*H*-pyrrole-3-sulfonamide.

- 141 -

Following the method of Example 191, the compound of Example 208 was made by preparation of 5-chloro-1*H*-indole-3-carbaldehyde (1-methyl-2,6-dioxo-3-propyl-1,2,3,6-tetrahydropyrimidin-4-yl)hydrazone and condensation with 5-formyl-*N*,1-dimethyl-1*H*-pyrrole-3-sulfonamide.

5

Following the method of Example 191, the compound of Example 209 was made by preparation of 5-chloro-1*H*-indole-3-carbaldehyde [3-(cyclopropylmethyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl]hydrazone and condensation with *N*-[(5-formyl-1-methyl-1*H*-pyrrol-3-yl)sulfonyl]glycine.

10

Following the method of Example 191, the compound of Example 210 was made by preparation of 5-methyl-3*a*,7*a*-dihydro-1*H*-indole-3-carbaldehyde (3-isobutyl-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)hydrazone and condensation with *N*-[(5-formyl-1-methyl-1*H*-pyrrol-3-yl)sulfonyl]glycine.

15

Following the method of Example 191, the compound of Example 211 was made by preparation of 5-chloro-1*H*-indole-3-carbaldehyde [3-isobutyl-1-(2-morpholin-4-ylethyl)-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl]hydrazone and condensation with 1-methyl-1*H*-imidazole-5-carbaldehyde.

20

Following the method of Example 191, the compound of Example 212 was made by preparation of 5-fluoro-1-benzothiophene-3-carbaldehyde (3-isobutyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)hydrazone and condensation with isonicotinaldehyde.

25 Following the method of Example 191, the compound of Example 213 was made by preparation of 5-chloro-1-benzothiophene-3-carbaldehyde (3-isobutyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)hydrazone and condensation with isonicotinaldehyde.

Following the method of Example 191, the compound of Example 214 was made by
30 preparation of 5-chloro-1-benzothiophene-3-carbaldehyde (3-isobutyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)hydrazone and condensation with 1-methyl-1*H*-imidazole-2-carbaldehyde.

- 142 -

Following the method of Example 191, the compound of Example 215 was made by preparation of 5-fluoro-1-benzothiophene-3-carbaldehyde (3-isobutyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)hydrazone and condensation with 1-methyl-1*H*-imidazole-2-carbaldehyde.

5

Following the method of Example 191, the compound of Example 216 was made by preparation of 5-fluoro-1-benzothiophene-3-carbaldehyde (3-isobutyl-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)hydrazone and condensation with 1-methyl-1*H*-pyrrole-2-carbaldehyde.

10

Following the method of Example 191, the compound of Example 217 was made by preparation of 5-fluoro-1-benzothiophene-3-carbaldehyde (3-isobutyl-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)hydrazone and condensation with isonicotinaldehyde.

15 Following the method of Example 191, the compound of Example 218 was made by preparation of 5-chloro-1*H*-indole-3-carbaldehyde (3-isobutyl-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)hydrazone and condensation with *N*-(5-formylpyridin-2-yl)acetamide.

20 Following the method of Example 191, the compound of Example 219 was made by preparation of 5-fluoro-1-benzothiophene-3-carbaldehyde (3-isobutyl-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)hydrazone and condensation with *N*-(5-formylpyridin-2-yl)acetamide.

25 Following the method of Example 191, the compound of Example 220 was made by preparation of 5-fluoro-1-benzothiophene-3-carbaldehyde (3-isobutyl-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)hydrazone and condensation with 1-methyl-1*H*-pyrrole-2-carbaldehyde.

30 Following the method of Example 191, the compound of Example 221 was made by preparation of 5-chloro-1*H*-indole-3-carbaldehyde (3-isobutyl-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)hydrazone and condensation with 4-methyl-4*H*-1,2,4-triazole-3-carbaldehyde.

- 143 -

Following the method of Example 191, the compound of Example 222 was made by preparation of 5-methyl-3a,7a-dihydro-1*H*-indole-3-carbaldehyde (3-isobutyl-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)hydrazone and condensation with 4-methyl-4*H*-1,2,4-triazole-3-carbaldehyde.

Following the method of Example 191, the compound of Example 223 was made by preparation of 5-methyl-3a,7a-dihydro-1*H*-indole-3-carbaldehyde [3-(cyclopropylmethyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl]hydrazone and condensation with 4-methyl-4*H*-1,2,4-triazole-3-carbaldehyde.

Following the method of Example 191, the compound of Example 224 was made by preparation of 5-chloro-1*H*-indole-3-carbaldehyde [3-(cyclopropylmethyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl]hydrazone and condensation with 4-methyl-4*H*-1,2,4-triazole-3-carbaldehyde.

Following the method of Example 191, the compound of Example 225 was made by preparation of 5-chloro-1*H*-indazole-3-carbaldehyde (3-isobutyl-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)hydrazone and condensation with 1-methyl-1*H*-imidazole-2-carbaldehyde.

Following the method of Example 191, the compound of Example 226 was made by preparation of 5-chloro-1*H*-indazole-3-carbaldehyde [3-(cyclopropylmethyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl]hydrazone and condensation with 1-methyl-1*H*-imidazole-2-carbaldehyde.

Following the method of Example 191, the compound of Example 227 was made by preparation of 5-fluoro-1-benzothiophene-3-carbaldehyde (3-isobutyl-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)hydrazone and condensation with 4-methyl-4*H*-1,2,4-triazole-3-carbaldehyde.

Following the method of Example 191, the compound of Example 228 was made by preparation of 5-chloro-1*H*-indazole-3-carbaldehyde (3-isobutyl-1-methyl-2,6-dioxo-1,2,3,6-

- 144 -

tetrahydropyrimidin-4-yl]hydrazone and condensation with 4-methyl-4*H*-1,2,4-triazole-3-carbaldehyde.

Following the method of Example 191, the compound of Example 229 was made by
5 preparation of 6-chloroquinoline-4-carbaldehyde (3-isobutyl-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl]hydrazone and condensation with 4-methyl-4*H*-1,2,4-triazole-3-carbaldehyde.

Following the method of Example 191, the compound of Example 230 was made by
10 preparation of 5-fluoro-1-benzothiophene-3-carbaldehyde [3-(cyclopropylmethyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl]hydrazone and condensation with 4-methyl-4*H*-1,2,4-triazole-3-carbaldehyde.

Following the method of Example 191, the compound of Example 231 was made by
15 preparation of 5-chloro-1*H*-indazole-3-carbaldehyde [3-(cyclopropylmethyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl]hydrazone and condensation with 4-methyl-4*H*-1,2,4-triazole-3-carbaldehyde.

Following the method of Example 191, the compound of Example 232 was made by
20 preparation of 6-chloroquinoline-4-carbaldehyde [3-(cyclopropylmethyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl]hydrazone and condensation with 4-methyl-4*H*-1,2,4-triazole-3-carbaldehyde.

Following the method of Example 191, the compound of Example 233 was made by
25 preparation of 5-chloro-1*H*-indole-3-carbaldehyde (3-isobutyl-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl]hydrazone and condensation with 4-bromo-1-methyl-1*H*-pyrrole-2-carbaldehyde (Kaye, P. T.; Macrae, R.; Meakins, G. D.; Patterson, C. H. *J.Chem.Soc.Perkin Trans.2* 1980, 1631-1635).

Following the method of Example 191, the compound of Example 234 was made by
30 preparation of 5-chloro-1*H*-indole-3-carbaldehyde [3-(cyclopropylmethyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl]hydrazone and condensation with 1-methyl-4-(methylsulfinyl)-1*H*-pyrrole-2-carbaldehyde.

- 145 -

Following the method of Example 191, the compound of Example 235 was made by preparation of 5-fluoro-1-benzothiophene-3-carbaldehyde [3-(cyclopropylmethyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl]hydrazone and condensation with 1-methyl-4-
5 (methylsulfinyl)-1*H*-pyrrole-2-carbaldehyde.

Following the method of Example 191, the compound of Example 236 was made by preparation of 5-methyl-3a,7a-dihydro-1*H*-indole-3-carbaldehyde [3-(cyclopropylmethyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl]hydrazone and condensation with 1-
10 methyl-4-(methylsulfinyl)-1*H*-pyrrole-2-carbaldehyde.

Following the method of Example 191, the compound of Example 237 was made by preparation of 5-chloro-1*H*-indole-3-carbaldehyde (3-isobutyl-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)hydrazone and condensation with 1-methyl-4-(methylsulfinyl)-1*H*-
15 pyrrole-2-carbaldehyde.

Following the method of Example 191, the compound of Example 238 was made by preparation of 5-methyl-3a,7a-dihydro-1*H*-indole-3-carbaldehyde (3-isobutyl-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)hydrazone and condensation with 1-methyl-4-
20 (methylsulfinyl)-1*H*-pyrrole-2-carbaldehyde.

Following the method of Example 191, the compound of Example 239 was made by preparation of 6-chloroquinoline-4-carbaldehyde (3-isobutyl-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)hydrazone and condensation with 1-methyl-4-(methylsulfinyl)-1*H*-
25 pyrrole-2-carbaldehyde.

Following the method of Example 191, the compound of Example 240 was made by preparation of 6-chloroquinoline-4-carbaldehyde [3-(cyclopropylmethyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl]hydrazone and condensation with 1-methyl-4-
30 (methylsulfinyl)-1*H*-pyrrole-2-carbaldehyde.

Following the method of Example 191, the compound of Example 241 was made by preparation of 5-methyl-3a,7a-dihydro-1*H*-indole-3-carbaldehyde [3-(cyclopropylmethyl)-1-

- 146 -

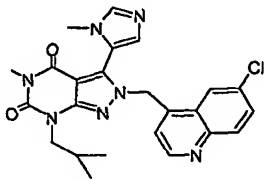
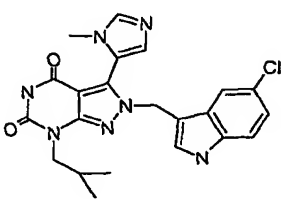
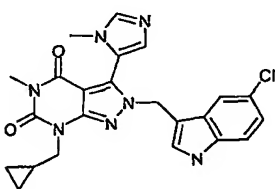
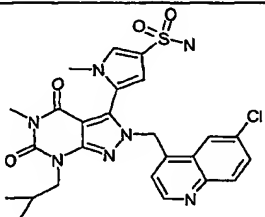
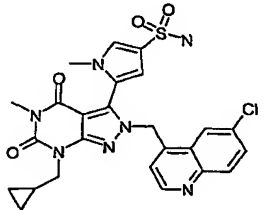
methyl-2,6-dioxo-1,2,3,6- tetrahydropyrimidin-4-yl]hydrazone and condensation with 1-methyl-4-(methylthio)-1*H*-pyrrole-2-carbaldehyde.

Following the method of Example 191, the compound of Example 242 was made by
5 preparation of 5-chloro-1*H*-indole-3-carbaldehyde [3-(cyclopropylmethyl)-1-methyl-2,6-dioxo-1,2,3,6- tetrahydropyrimidin-4-yl]hydrazone and condensation with 1-methyl-4-(methylsulfonyl)-1*H*-pyrrole-2-carbaldehyde.

Following the method of Example 191, the compound of Example 243 was made by
10 preparation of 5-methyl-3a,7a-dihydro-1*H*-indole-3-carbaldehyde [3-(cyclopropylmethyl)-1-methyl-2,6-dioxo-1,2,3,6- tetrahydropyrimidin-4-yl]hydrazone and condensation with 1-methyl-4-(methylsulfonyl)-1*H*-pyrrole-2-carbaldehyde.

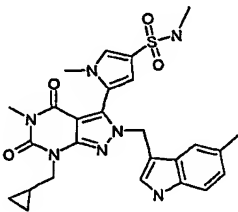
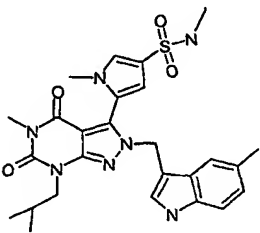
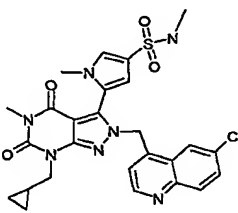
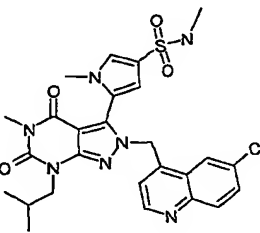
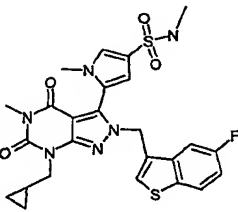
Following the method of Example 191, the compound of Example 244 was made by
15 preparation of 5-fluoro-1-benzothiophene-3-carbaldehyde [3-(cyclopropylmethyl)-1-methyl-2,6-dioxo-1,2,3,6- tetrahydropyrimidin-4-yl]hydrazone and condensation with 1-methyl-4-(methylsulfonyl)-1*H*-pyrrole-2-carbaldehyde.

Following the method of Example 191, the compound of Example 245 was made by
20 preparation of 6-chloroquinoline-4-carbaldehyde 3-(cyclopropylmethyl)-1-methyl-2,6-dioxo-1,2,3,6- tetrahydropyrimidin-4-yl]hydrazone and condensation with 1-methyl-4-(methylsulfonyl)-1*H*-pyrrole-2-carbaldehyde.

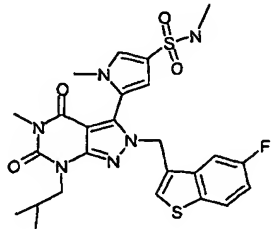
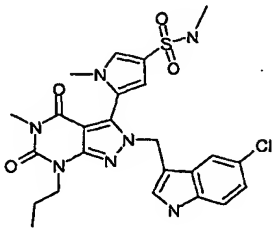
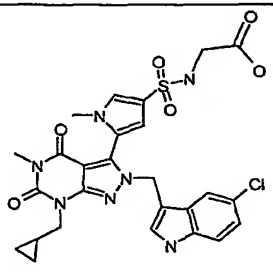
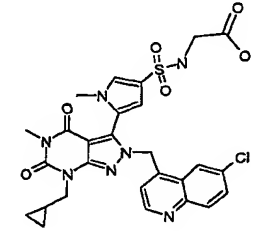
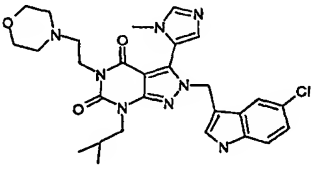
Example	Structure	Name	ES ⁺ (M+H)
192		2-[(6-chloroquinolin-4-yl)methyl]-7-isobutyl-5-methyl-3-(1-methyl-1H-imidazol-5-yl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione	478.21
193		2-[(5-chloro-1H-indol-3-yl)methyl]-7-isobutyl-3-(1-methyl-1H-imidazol-5-yl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione	452.17
194		2-[(5-chloro-1H-indol-3-yl)methyl]-7-(cyclopropylmethyl)-5-methyl-3-(1-methyl-1H-imidazol-5-yl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione	464.19
195		5-{2-[(6-chloroquinolin-4-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl}-1-methyl-1H-pyrrole-3-sulfonamide	556.07
196		5-[2-[(6-chloroquinolin-4-yl)methyl]-7-(cyclopropylmethyl)-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]-1-methyl-1H-pyrrole-3-sulfonamide	554.07

- 148 -

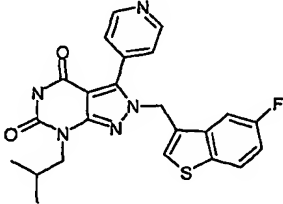
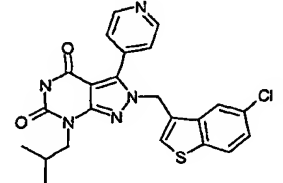
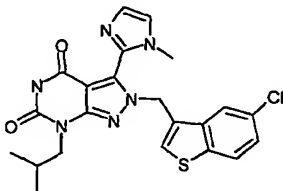
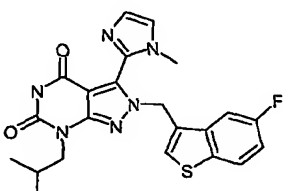
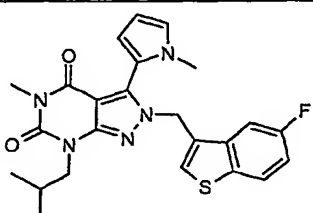
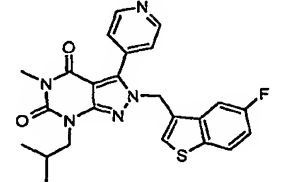
197		2-[(5-chloro-1 <i>H</i> -indol-3-yl)methyl]-7-isobutyl-5-methyl-3-[1-methyl-4-(methylsulfonyl)-1 <i>H</i> -imidazol-2-yl]-2 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidine-4,6(5 <i>H</i> ,7 <i>H</i>)-dione	544.05
198		2-[(5-chloro-1 <i>H</i> -indol-3-yl)methyl]-7-(cyclopropylmethyl)-5-methyl-3-[1-methyl-4-(methylsulfonyl)-1 <i>H</i> -imidazol-2-yl]-2 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidine-4,6(5 <i>H</i> ,7 <i>H</i>)-dione	542.05
199		5-{2-[(6-chloroquinolin-4-yl)methyl]-5-methyl-4,6-dioxo-7-propyl-4,5,6,7-tetrahydro-2 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl}- <i>N</i> ,1-dimethyl-1 <i>H</i> -pyrrole-3-sulfonamide	556.18
200		5-[2-[(5-chloro-1 <i>H</i> -indol-3-yl)methyl]-7-(cyclopropylmethyl)-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl]- <i>N</i> ,1-dimethyl-1 <i>H</i> -pyrrole-3-sulfonamide	556.09
201		5-{2-[(5-chloro-1 <i>H</i> -indol-3-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl}- <i>N</i> ,1-dimethyl-1 <i>H</i> -pyrrole-3-sulfonamide	558.03

202		5-{7-(cyclopropylmethyl)-5-methyl-2-[(5-methyl-1H-indol-3-yl)methyl]-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl}-N,1-dimethyl-1H-pyrrole-3-sulfonamide	536.18
203		5-{7-isobutyl-5-methyl-2-[(5-methyl-1H-indol-3-yl)methyl]-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl}-N,1-dimethyl-1H-pyrrole-3-sulfonamide	538.16
204		5-[2-[(6-chloroquinolin-4-yl)methyl]-7-(cyclopropylmethyl)-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]-N,1-dimethyl-1H-pyrrole-3-sulfonamide	568.16
205		5-{2-[(6-chloroquinolin-4-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl}-N,1-dimethyl-1H-pyrrole-3-sulfonamide	570.17
206		5-{7-(cyclopropylmethyl)-2-[(5-fluoro-1-benzothien-3-yl)methyl]-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl}-N,1-dimethyl-1H-pyrrole-3-sulfonamide	557.17

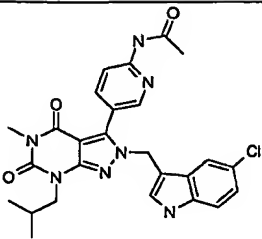
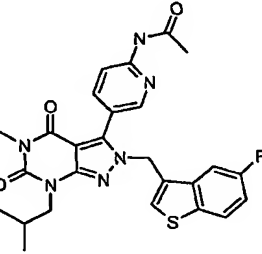
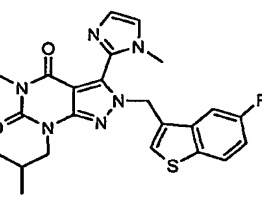
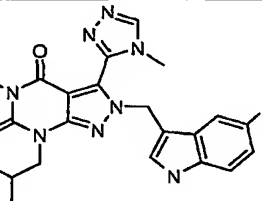
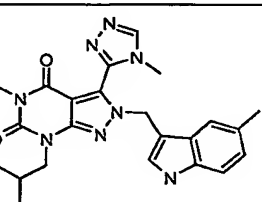
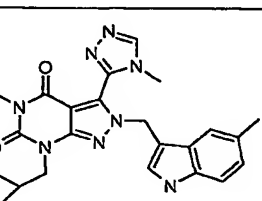
- 150 -

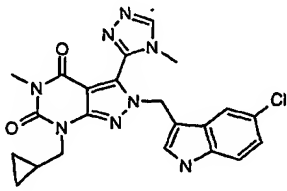
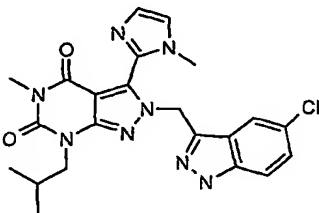
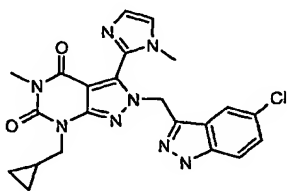
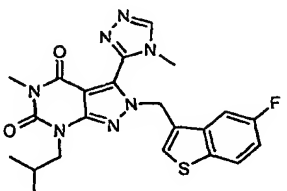
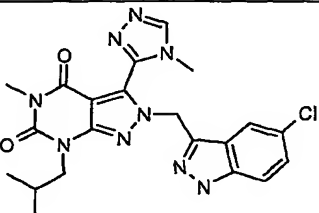
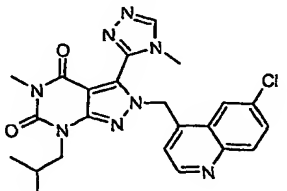
207		5-{2-[(5-fluoro-1-benzothien-3-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl}-N,1-dimethyl-1H-pyrrole-3-sulfonamide	559.15
208		5-{2-[(5-chloro-1H-indol-3-yl)methyl]-5-methyl-4,6-dioxo-7-propyl-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl}-N,1-dimethyl-1H-pyrrole-3-sulfonamide	544.04
209		N-({5-[2-[(5-chloro-1H-indol-3-yl)methyl]-7-(cyclopropylmethyl)-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]-1-methyl-1H-pyrrol-3-yl}sulfonyl)glycine	600.08
210		N-({5-[2-[(6-chloroquinolin-4-yl)methyl]-7-(cyclopropylmethyl)-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]-1-methyl-1H-pyrrol-3-yl}sulfonyl)glycine	612.11
211		2-[(5-chloro-1H-indol-3-yl)methyl]-7-isobutyl-3-(1-methyl-1H-imidazol-5-yl)-5-(2-morpholin-4-ylethyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione	565.22

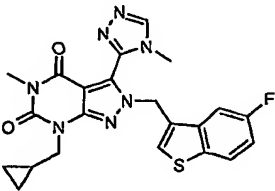
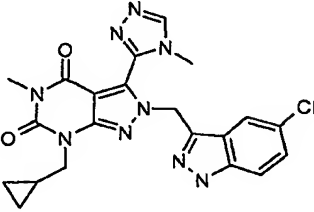
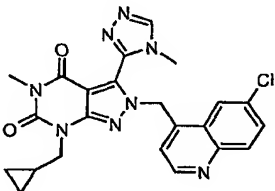
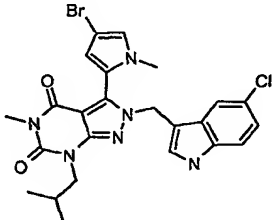
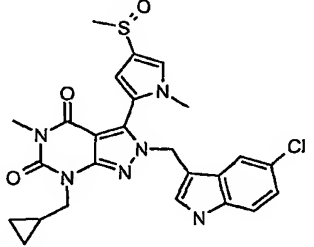
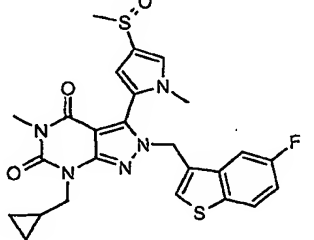
- 151 -

212		2-[(5-fluoro-1-benzothien-3-yl)methyl]-7-isobutyl-3-pyridin-4-yl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione	450.18
213		2-[(5-chloro-1-benzothien-3-yl)methyl]-7-isobutyl-3-pyridin-4-yl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione	466.23
214		2-[(5-chloro-1-benzothien-3-yl)methyl]-7-isobutyl-3-(1-methyl-1H-imidazol-2-yl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione	469.27
215		2-[(5-fluoro-1-benzothien-3-yl)methyl]-7-isobutyl-3-(1-methyl-1H-imidazol-2-yl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione	453.14
216		2-[(5-fluoro-1-benzothien-3-yl)methyl]-7-isobutyl-5-methyl-3-(1-methyl-1H-pyrrol-2-yl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione	466.18
217		2-[(5-fluoro-1-benzothien-3-yl)methyl]-7-isobutyl-5-methyl-3-pyridin-4-yl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione	464.18

- 152 -

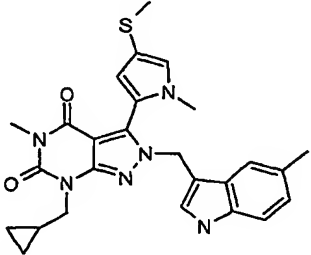
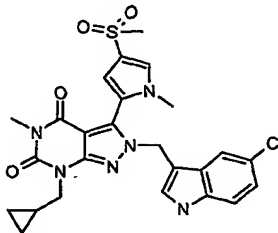
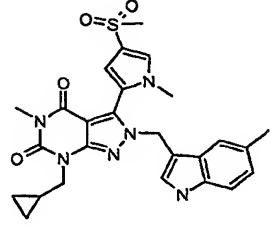
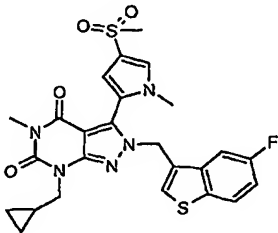
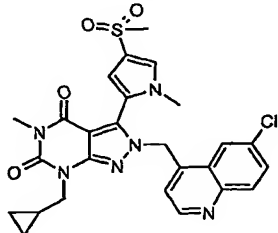
218		N-(5-{2-[(5-chloro-1H-indol-3-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl}pyridin-2-yl)acetamide	520.07
219		N-(5-{2-[(5-fluoro-1-benzothien-3-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl}pyridin-2-yl)acetamide	521.08
220		2-[(5-fluoro-1-benzothien-3-yl)methyl]-7-isobutyl-5-methyl-3-(1-methyl-1H-imidazol-2-yl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione	467.21
221		2-[(5-chloro-1H-indol-3-yl)methyl]-7-isobutyl-5-methyl-3-(4-methyl-4H-1,2,4-triazol-3-yl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione	467.09
222		7-isobutyl-5-methyl-2-[(5-methyl-1H-indol-3-yl)methyl]-3-(4-methyl-4H-1,2,4-triazol-3-yl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione	447.20
223		7-(cyclopropylmethyl)-5-methyl-2-[(5-methyl-1H-indol-3-yl)methyl]-3-(4-methyl-4H-1,2,4-triazol-3-yl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione	445.23

224		2-[(5-chloro-1H-indol-3-yl)methyl]-7-(cyclopropylmethyl)-5-methyl-3-(4-methyl-4H-1,2,4-triazol-3-yl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione	465.12
225		2-[(5-chloro-1H-indazol-3-yl)methyl]-7-isobutyl-5-methyl-3-(1-methyl-1H-imidazol-2-yl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione	467.12
226		2-[(5-chloro-1H-indazol-3-yl)methyl]-7-(cyclopropylmethyl)-5-methyl-3-(1-methyl-1H-imidazol-2-yl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione	465.11
227		2-[(5-fluoro-1-benzothien-3-yl)methyl]-7-isobutyl-5-methyl-3-(4-methyl-4H-1,2,4-triazol-3-yl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione	468.21
228		2-[(5-chloro-1H-indazol-3-yl)methyl]-7-isobutyl-5-methyl-3-(4-methyl-4H-1,2,4-triazol-3-yl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione	468.22
229		2-[(6-chloroquinolin-4-yl)methyl]-7-isobutyl-5-methyl-3-(4-methyl-4H-1,2,4-triazol-3-yl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione	479.22

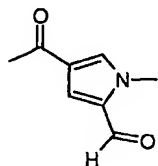
230		7-(cyclopropylmethyl)-2-[(5-fluoro-1-benzothien-3-yl)methyl]-5-methyl-3-(4-methyl-4H-1,2,4-triazol-3-yl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione	466.20
231		2-[(5-chloro-1H-indazol-3-yl)methyl]-7-(cyclopropylmethyl)-5-methyl-3-(4-methyl-4H-1,2,4-triazol-3-yl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione	466.20
232		2-[(6-chloroquinolin-4-yl)methyl]-7-(cyclopropylmethyl)-5-methyl-3-(4-methyl-4H-1,2,4-triazol-3-yl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione	477.22
233		3-(4-bromo-1-methyl-1H-pyrrol-2-yl)-2-[(5-chloro-1H-indol-3-yl)methyl]-7-isobutyl-5-methyl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione	543.19
234		2-[(5-chloro-1H-indol-3-yl)methyl]-7-(cyclopropylmethyl)-5-methyl-3-[1-methyl-4-(methylsulfinyl)-1H-pyrrol-2-yl]-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione	525.09
235		7-(cyclopropylmethyl)-2-[(5-fluoro-1-benzothien-3-yl)methyl]-5-methyl-3-[1-methyl-4-(methylsulfinyl)-1H-pyrrol-2-yl]-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione	526.09

236		7-(cyclopropylmethyl)-5-methyl-2-[(5-methyl-1H-indol-3-yl)methyl]-3-[1-methyl-4-(methylsulfinyl)-1H-pyrrol-2-yl]-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione	505.12
237		2-[(5-chloro-1H-indol-3-yl)methyl]-7-isobutyl-5-methyl-3-[1-methyl-4-(methylsulfinyl)-1H-pyrrol-2-yl]-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione	527.09
238		7-isobutyl-5-methyl-2-[(5-methyl-1H-indol-3-yl)methyl]-3-[1-methyl-4-(methylsulfinyl)-1H-pyrrol-2-yl]-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione	507.13
239		2-[(6-chloroquinolin-4-yl)methyl]-7-isobutyl-5-methyl-3-[1-methyl-4-(methylsulfinyl)-1H-pyrrol-2-yl]-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione	539.11
240		2-[(6-chloroquinolin-4-yl)methyl]-7-(cyclopropylmethyl)-5-methyl-3-[1-methyl-4-(methylsulfinyl)-1H-pyrrol-2-yl]-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione	537.11

- 156 -

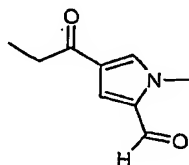
241		7-(cyclopropylmethyl)-5-methyl-2-[(5-methyl-1H-indol-3-yl)methyl]-3-[1-methyl-4-(methylthio)-1H-pyrrol-2-yl]-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione	489.20
242		2-[(5-chloro-1H-indol-3-yl)methyl]-7-(cyclopropylmethyl)-5-methyl-3-[1-methyl-4-(methylsulfonyl)-1H-pyrrol-2-yl]-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione	541.12
243		7-(cyclopropylmethyl)-5-methyl-2-[(5-methyl-1H-indol-3-yl)methyl]-3-[1-methyl-4-(methylsulfonyl)-1H-pyrrol-2-yl]-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione	521.15
244		7-(cyclopropylmethyl)-2-[(5-fluoro-1-benzothien-3-yl)methyl]-5-methyl-3-[1-methyl-4-(methylsulfonyl)-1H-pyrrol-2-yl]-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione	542.05
245		2-[(6-chloroquinolin-4-yl)methyl]-7-(cyclopropylmethyl)-5-methyl-3-[1-methyl-4-(methylsulfonyl)-1H-pyrrol-2-yl]-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione	551.13

- 157 -

Example 246**Preparation of 4-acetyl-1-methyl-1H-pyrrole-2-carbaldehyde**

5

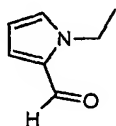
To a suspension of aluminium chloride (22.9g, 172 mmol) in anhydrous dichloromethane (100ml) and acetylchloride (4.5g, 57.3mmol) was added a solution of 1- methyl pyrrole-2-carboxaldehyde (5g, 46mmol) in anhydrous dichloromethane (20ml). The mixture was refluxed for 90min, poured into ice and stirred until melted. The layers were separated and aqueous layer was extracted with dichloromethane (2x100ml). The organic phase and extracts were combined, dried over sodium sulfate. The solvent was removed *in vacuo* to give the title compound (6.8g, 94%), ¹H NMR (d6-DMSO) δ 9.6 (s, 1H), 7.9 (s, 1H), 7.4 (s, 1H), 3.9 (s, 3H), 2.4 (s, 3H)

15 **Example 247****Preparation of 1-methyl-4-propionyl-1H-pyrrole-2-carbaldehyde**

20 To a suspension of aluminium chloride (22.9g, 172 mmol) in anhydrous dichloromethane (100ml) and propionylchloride (5.3g, 57.3mmol) was added a solution of 1- methyl pyrrole-2-carboxaldehyde (5g, 46mmol) in anhydrous dichloromethane (20ml). The mixture was refluxed for 90min, poured into ice and stirred until melted. The layers were separated and aqueous layer was extracted with dichloromethane (2x100ml). The organic phase and extracts were combined, dried over sodium sulfate. The solvent was removed *in vacuo* to give the title compound (7.2g, 95%), ¹H NMR (d6-DMSO) δ 9.6 (s, 1H), 7.9 (s, 1H), 7.4 (s, 1H), 3.9 (s, 3H), 2.8 (q, 2H), 1.06 (t, 3H).

Example 248**Preparation of 1 ethyl-1H-2-carbaldehyde**

5

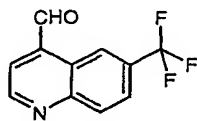


Lithium diisopropylamine (27ml, 53.3mmol) was cooled to -60°C under nitrogen gas. To the cooled solution was added dropwise N-ethylimidazole in anhydrous THF (5ml) at -50°C. The mixture was stirred at low temperature for 2h, cooled to -70°C and N, N-dimethylformamide (5ml) added rapidly over a few minutes and warmed to room temperature. A solution of sodium dihydrogen phosphate was added to a cooled solution and aqueous layer was separated, filtered and the filtrate was extracted with dichloromethane (3x100ml). The combined organic phase was dried over sodium sulfate, filtered and concentrated in vacuo to give a brown oil which was distilled giving the title compound (4.2g). ¹H NMR (CDCl₃) δ 9.8 (s, 1H), 7.3 (s, 1H), 7.18(s, 1H), 4.44 (q, 2H), 1.14 (t, 3H).

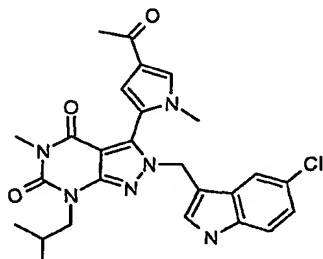
15

Example 249**Preparation of 6-trifluoromethylquinoline-4-carboxaldehyde**

20

**Example 250**

25



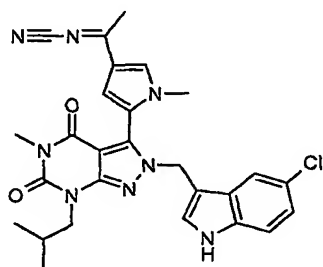
- 159 -

3-(4-acetyl-1-methyl-1H-pyrrol-2-yl)-2-[(5-chloro-1H-indol-3-yl)methyl]-7-isobutyl-5-methyl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione

This compound was made following the procedure described above, starting with 6-hydrazino-1-isobutyl-3-methylpyrimidine-2,4(1H,3H)-dione and condensing first with 5-chloro-1H-indole-3-carbaldehyde, followed by 4-acetyl-1-methyl-1H-pyrrole-2-carbaldehyde. 508.5 (M+H).

Example 251

1-(5-{2-[(5-chloro-1H-indol-3-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl}-1-methyl-1H-pyrrol-3-yl)ethylenecyanamide

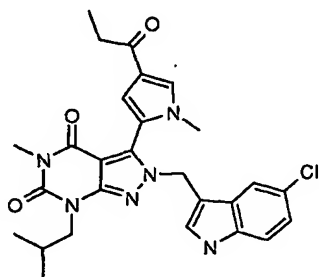


This compound was made in two steps following the procedure described above, starting with 6-hydrazino-1-isobutyl-3-methylpyrimidine-2,4(1H,3H)-dione, and condensing first 5-chloro-1H-indole-3-carbaldehyde, followed by 4-acetyl-1-methyl-1H-pyrrole-2-carbaldehyde. The isolated 3-(4-acetyl-1-methyl-1H-pyrrol-2-yl)-2-[(5-chloro-1H-indol-3-yl)methyl]-7-isobutyl-5-methyl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione was treated with a cold solution of bis(trimethylsilyl)carbodiimide and TiCl₄ at 0°C in anhydrous dichloromethane. The mixture was stirred at room temperature for 4h. The crude reaction product was purified by semi-prep RPHPLC eluting with water/acetonitrile/trifluoroacetic acid mixtures. 531.2 (M+H).

Example 252

- 160 -

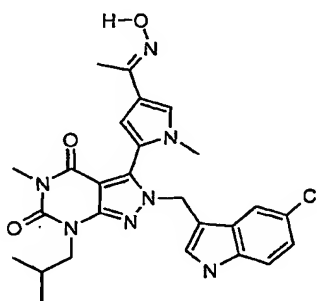
2-[(5-chloro-1H-indol-3-yl)methyl]-7-isobutyl-5-methyl-3-(1-methyl-4-propionyl-1H-pyrrol-2-yl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione



This compound was made following the procedure described above, starting with 6-hydrazino-1-isobutyl-3-methylpyrimidine-2,4(1*H*,3*H*)-dione and condensing first with 5-chloro-1*H*-indole-3-carbaldehyde, followed by 1-methyl-4-propionyl-1*H*-pyrrole-2-carbaldehyde. 521 (M+H).

Example 253

2-[(5-chloro-1H-indol-3-yl)methyl]-3-{4-[(1*E*)-N-hydroxyethanimidoyl]-1-methyl-1H-pyrrol-2-yl}-7-isobutyl-5-methyl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione



This compound was made in one pot following the procedure described above, starting with 6-hydrazino-1-isobutyl-3-methylpyrimidine-2,4(1*H*,3*H*)-dione, and condensing first 5-chloro-1*H*-indole-3-carbaldehyde, followed by 4-acetyl-1-methyl-1*H*-pyrrole-2-carbaldehyde. To the crude 3-(4-acetyl-1-methyl-1*H*-pyrrol-2-yl)-2-[(5-chloro-1*H*-indol-3-yl)methyl]-7-isobutyl-5-methyl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione was treated with hydroxylamine hydrochloride and heated at 80°C in *N,N'*-Dimethylacetamide for 18h. The crude reaction

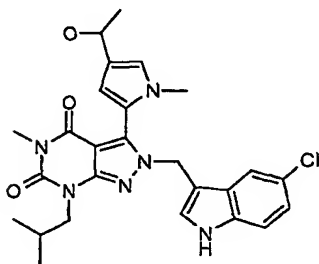
- 161 -

product was purified by semi-prep RPHPLC eluting with water/acetonitrile /trifluoroacetic acid mixtures. 522 (M+H).

Example 254

5

2-[(5-chloro-1H-indol-3-yl)methyl]-3-[4-(1-hydroxyethyl)-1-methyl-1H-pyrrol-2-yl]-7-isobutyl-5-methyl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione



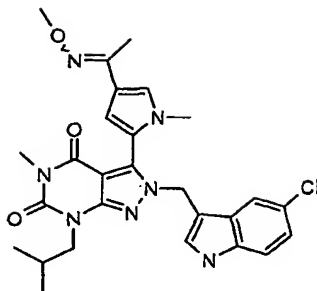
- 10 This compound was made in two steps following the procedure described above, starting with 6-hydrazino-1-isobutyl-3-methylpyrimidine-2,4(1*H*,3*H*)-dione, and condensing first 5-chloro-1*H*-indole-3-carbaldehyde, followed by 4-acetyl-1-methyl-1*H*-pyrrole-2-carbaldehyde. The isolated 3-(4-acetyl-1-methyl-1*H*-pyrrol-2-yl)-2-[(5-chloro-1*H*-indol-3-yl)methyl]-7-isobutyl-5-methyl-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione was treated sodium borohydride in
- 15 anhydrous THF and heated at 80°C for 1h and the product was isolated by aqueous workup. The presence of alcohol peak (δ 64.8ppm) was confirmed by ^{13}C NMR (CDCl_3)- no ketone peak at (δ 193.5ppm).

Example 255

20

2-[(5-chloro-1H-indol-3-yl)methyl]-7-isobutyl-3-{4-[(1*E*)-*N*-methoxyethanimidoyl]-1-methyl-1*H*-pyrrol-2-yl}-5-methyl-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione

- 162 -

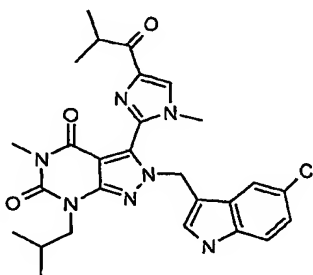


This compound was made following the procedure described above, starting with 6-hydrazino-1-isobutyl-3-methylpyrimidine-2,4(1*H*,3*H*)-dione, and condensing first 5-chloro-1*H*-indole-3-carbaldehyde, followed by 4-acetyl-1-methyl-1*H*-pyrrole-2-carbaldehyde. To the isolated 3-(4-acetyl-1-methyl-1*H*-pyrrol-2-yl)-2-[(5-chloro-1*H*-indol-3-yl)methyl]-7-isobutyl-5-methyl-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione was added 4 equivalents of methoxyamine hydrochloride, triethylamine and heated at 80°C in *N,N'*-dimethylacetamide for 4h. The mixture was stirred at room temperature for 4h. The crude reaction product was purified by semi-prep RPHPLC eluting with water/acetonitrile/trifluoroacetic acid mixtures.

536.2 (M+H).

Example 256

2-[(5-chloro-1*H*-indol-3-yl)methyl]-7-isobutyl-3-(4-isobutyryl-1-methyl-1*H*-imidazol-2-yl)-5-methyl-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione



This compound was made following the procedure described above, starting with 6-hydrazino-1-isobutyl-3-methylpyrimidine-2,4(1*H*,3*H*)-dione, and condensing first 5-chloro-1*H*-indole-3-carbaldehyde, followed by 4-isobutyryl-1-methyl-1*H*-imidazole-2-carbaldehyde.

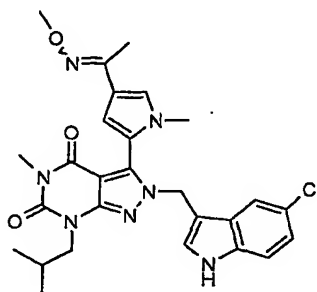
536 (M+H).

- 163 -

Example 257

2-[(5-chloro-1H-indol-3-yl)methyl]-7-isobutyl-3-{4-[(1E)-N-methoxyethanimidoyl]-1-methyl-1H-pyrrol-2-yl}-5-methyl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione

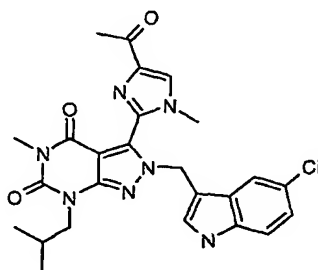
5



This compound was made in two steps following the procedure described above, starting with 6-hydrazino-1-isobutyl-3-methylpyrimidine-2,4(1*H*,3*H*)-dione, and condensing first 5-chloro-1*H*-indole-3-carbaldehyde, followed by 4-acetyl-1-methyl-1*H*-pyrrole-2-carbaldehyde. To the isolated 3-(4-acetyl-1-methyl-1*H*-pyrrol-2-yl)-2-[(5-chloro-1*H*-indol-3-yl)methyl]-7-isobutyl-5-methyl-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione was added 4 equivalents of methoxyamine hydrochloride, triethylamine and heated at 80°C in *N,N'*-dimethylacetamide for 4h. A second peak, an isomer was isolated purification by semi-prep RPHPLC eluting with water/acetonitrile/trifluoroacetic acid mixtures. 536.2 (*M*+*H*).

Example 258

3-(4-acetyl-1-methyl-1H-imidazol-2-yl)-2-[(5-chloro-1H-indol-3-yl)methyl]-7-isobutyl-5-methyl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione

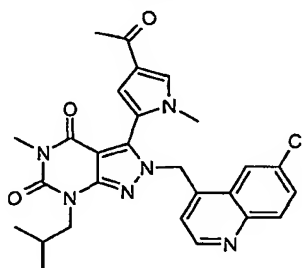


- 164 -

This compound was made following the procedure described above, starting 6-hydrazino-1-isobutyl-3-methylpyrimidine-2,4(1*H*,3*H*)-dione, and condensing first 5-chloro-1*H*-indole-3-carbaldehyde, followed by 4-acetyl-1-methyl-1*H*-imidazole-2-carbaldehyde. 508 (M+H).

5 Example 259

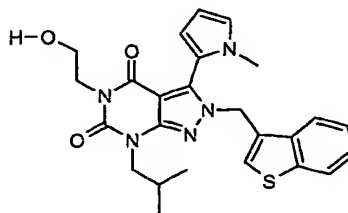
3-(4-acetyl-1-methyl-1*H*-pyrrol-2-yl)-2-[(6-chloroquinolin-4-yl)methyl]-7-isobutyl-5-methyl-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione



- 10 This compound was made following the procedure described above, starting with 6-hydrazino-1-isobutyl-3-methylpyrimidine-2,4(1*H*,3*H*)-dione, and condensing first with 6-chloroquinoline-4-carbaldehyde, followed by 4-acetyl-1-methyl-1*H*-pyrrole-2-carbaldehyde. 519 (M+H).

15 Example 260

2-(1-benzothien-3-ylmethyl)-5-(2-hydroxyethyl)-7-isobutyl-3-(1-methyl-1*H*-pyrrol-2-yl)-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione



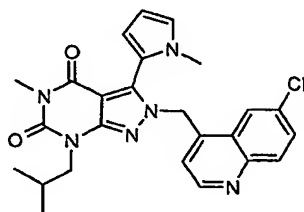
- 20 This compound was isolated as a byproduct from a two step preparation as described : A): 2-(1-benzothien-3-ylmethyl)-7-isobutyl-3-(1-methyl-1*H*-pyrrol-2-yl)-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione was prepared starting from 6-hydrazino-1-isobutylpyrimidine-2,4(1*H*,3*H*)-dione and condensing first with 1-benzothiophene-3-carbaldehyde, followed by 1-methyl-1*H*-pyrrole-2-carbaldehyde.

- 165 -

B): 2-(1-benzothien-3-ylmethyl)-7-isobutyl-3-(1-methyl-1*H*-pyrrol-2-yl)-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione was dissolved in anhydrous dimethylsulfoxide and 1,8-diazabicyclo[5.4.0]undec-7-ene was added. 1,2-dibromoethane was added and the mixture was heated at 80°C for 18h. The crude reaction product was purified by semi-prep RPHPLC
 5 eluting with water/acetonitrile/trifluoroacetic acid mixtures. 477 (M+H).

Example 261

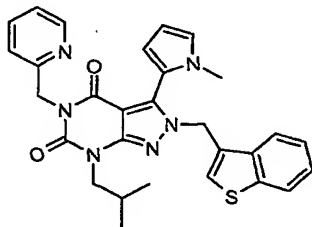
2-[(6-chloroquinolin-4-yl)methyl]-7-isobutyl-5-methyl-3-(1-methyl-1*H*-pyrrol-2-yl)-2*H*-
 10 pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione



This compound was made following the procedure described above, starting with 6-hydrazino-1-isobutyl-3-methylpyrimidine-2,4(1*H*,3*H*)-dione, and condensing first with 6-chloroquinoline-4-carbaldehyde, followed by 1-methyl-1*H*-pyrrole-2-carbaldehyde. 477.9
 15 (M+H).

Example 262

20 2-(1-benzothien-3-ylmethyl)-7-isobutyl-3-(1-methyl-1*H*-pyrrol-2-yl)-5-(pyridin-2-ylmethyl)-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione



This compound was obtained from a two step preparation as described : A): 2-(1-benzothien-3-ylmethyl)-7-isobutyl-3-(1-methyl-1*H*-pyrrol-2-yl)-2*H*-pyrazolo[3,4-*d*]pyrimidine-
 25 4,6(5*H*,7*H*)-dione was prepared starting from 6-hydrazino-1-isobutylpyrimidine-2,4(1*H*,3*H*)-

- 166 -

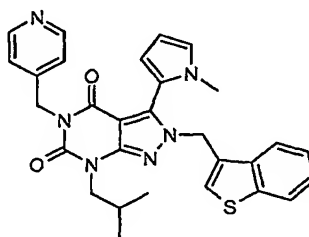
dione and condensing first with 1-benzothiophene-3-carbaldehyde, followed by 1-methyl-1*H*-pyrrole-2-carbaldehyde.

B): 2-(1-benzothien-3-ylmethyl)-7-isobutyl-3-(1-methyl-1*H*-pyrrol-2-yl)-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione was dissolved in anhydrous dimethylsulfoxide and 1,8-diazabicyclo[5.4.0]undec-7-ene was added. 2-picolyyl chloride hydrochloride was added and the mixture was heated at 80°C for 18h. The crude reaction product was purified by semi-prep RPHPLC eluting with water/acetonitrile/trifluoroacetic acid mixtures. 525 (M+H).

Example 263

10

2-(1-benzothien-3-ylmethyl)-7-isobutyl-3-(1-methyl-1*H*-pyrrol-2-yl)-5-(pyridin-2-ylmethyl)-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione



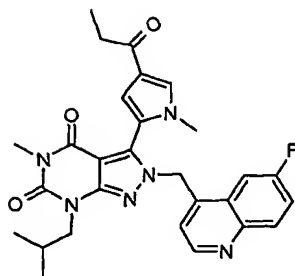
This compound was obtained from a two step preparation as described : A): 2-(1-benzothien-3-ylmethyl)-7-isobutyl-3-(1-methyl-1*H*-pyrrol-2-yl)-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione was prepared starting from 6-hydrazino-1-isobutylpyrimidine-2,4(1*H*,3*H*)-dione and condensing first with 1-benzothiophene-3-carbaldehyde, followed by 1-methyl-1*H*-pyrrole-2-carbaldehyde.

B): 2-(1-benzothien-3-ylmethyl)-7-isobutyl-3-(1-methyl-1*H*-pyrrol-2-yl)-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione was dissolved in anhydrous dimethylsulfoxide and 1,8-diazabicyclo[5.4.0]undec-7-ene was added. 4-chloromethylpyridine hydrochloride was added and the mixture was heated at 80°C for 18h. The crude reaction product was purified by semi-prep RPHPLC eluting with water/acetonitrile/trifluoroacetic acid mixtures. 525 (M+H).

Example 264

2-[(6-fluoroquinolin-4-yl)methyl]-7-isobutyl-5-methyl-3-(1-methyl-4-propionyl-1*H*-pyrrol-2-yl)-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione

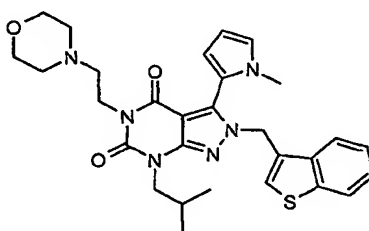
- 167 -



This compound was made following the procedure described above, starting with 6-hydrazino-1-isobutyl-3-methylpyrimidine-2,4(1*H*,3*H*)-dione, and condensing first with 6-fluoroquinoline-4-carbaldehyde, followed by 1-methyl-4-propionyl-1*H*-pyrrole-2-carbaldehyde. 517 (M+H).

Example 265

2-(1-benzothien-3-ylmethyl)-7-isobutyl-3-(1-methyl-1*H*-pyrrol-2-yl)-5-(2-morpholin-4-ylethyl)-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione

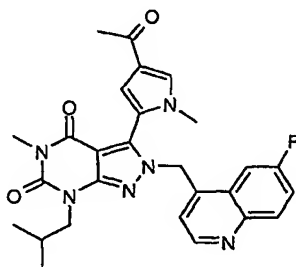


This compound was obtained from a two step preparation as described : A): 2-(1-benzothien-3-ylmethyl)-7-isobutyl-3-(1-methyl-1*H*-pyrrol-2-yl)-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione was prepared starting from 6-hydrazino-1-isobutylpyrimidine-2,4(1*H*,3*H*)-dione and condensing first with 1-benzothiophene-3-carbaldehyde, followed by 1-methyl-1*H*-pyrrole-2-carbaldehyde. B): 2-(1-benzothien-3-ylmethyl)-7-isobutyl-3-(1-methyl-1*H*-pyrrol-2-yl)-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione was dissolved in anhydrous dimethylsulfoxide and 1,8-diazabicyclo[5.4.0]undec-7-ene was added. 4-(2-chloroethyl)morpholine hydrochloride was added and the mixture was heated at 80°C for 18h. The crude reaction product was purified by semi-prep RPHPLC eluting with water/acetonitrile/trifluoroacetic acid mixtures. 547 (M+H).

- 168 -

Example 266

3-(4-acetyl-1-methyl-1H-pyrrol-2-yl)-2-[(6-fluoroquinolin-4-yl)methyl]-7-isobutyl-5-methyl-
 5 2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione

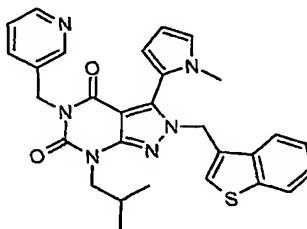


This compound was made following the procedure described above, starting with 6-
 10 hydrazino-1-isobutyl-3-methylpyrimidine-2,4(1H,3H)-dione, and condensing first with 6-fluoroquinoline-4-carbaldehyde, followed by 1-methyl-4-acetyl-1H-pyrrole-2-carbaldehyde.
 503(M+H).

Example 267

15

2-(1-benzothien-3-ylmethyl)-7-isobutyl-3-(1-methyl-1H-pyrrol-2-yl)-5-(pyridin-3-
 ylmethyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione



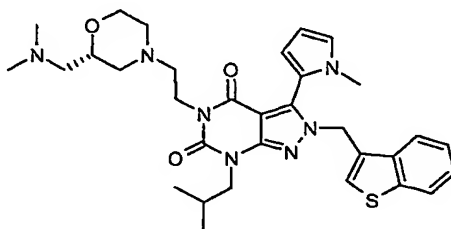
This compound was obtained from a two step preparation as described : A): 2-(1-benzothien-
 20 3-ylmethyl)-7-isobutyl-3-(1-methyl-1H-pyrrol-2-yl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione was prepared starting from 6-hydrazino-1-isobutylpyrimidine-2,4(1H,3H)-dione and condensing first with 1-benzothiophene-3-carbaldehyde, followed by 1-methyl-1H-pyrrole-2-carbaldehyde.

- 169 -

B): 2-(1-benzothien-3-ylmethyl)-7-isobutyl-3-(1-methyl-1*H*-pyrrol-2-yl)-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione was dissolved in anhydrous dimethylsulfoxide and 1,8-diazabicyclo[5.4.0]undec-7-ene was added. 3-chloromethylpyridine hydrochloride was added and the mixture was heated at 80°C for 18h. The crude reaction product was purified by semi-
 5 prep RPHPLC eluting with water/acetonitrile/trifluoroacetic acid mixtures. 525 (M+H).

Example 268

2-(1-benzothien-3-ylmethyl)-5-(2-{(2*S*)-2-[(dimethylamino)methyl]morpholin-4-
 10 yl}ethyl)-7-isobutyl-3-(1-methyl-1*H*-pyrrol-2-yl)-2*H*-pyrazolo[3,4-*d*]pyrimidine-
 4,6(5*H*,7*H*)-dione



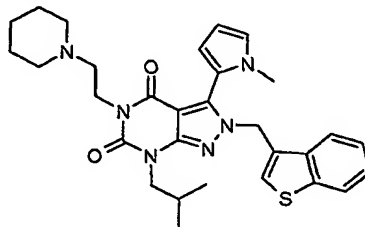
This compound was isolated from a three step preparation as described : A): 2-(1-benzothien-3-ylmethyl)-7-isobutyl-3-(1-methyl-1*H*-pyrrol-2-yl)-2*H*-pyrazolo[3,4-*d*]pyrimidine-
 15 4,6(5*H*,7*H*)-dione was prepared starting from 6-hydrazino-1-isobutylpyrimidine-2,4(1*H*,3*H*)-
 dione and condensing first with 1-benzothiophene-3-carbaldehyde, followed by 1-methyl-1*H*-
 pyrrole-2-carbaldehyde.

B): 2-(1-benzothien-3-ylmethyl)-7-isobutyl-3-(1-methyl-1*H*-pyrrol-2-yl)-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione was dissolved in anhydrous dimethylsulfoxide and cooled to
 20 0°C. To the solution was added sodium hydride until effervescence stopped. To the mixture
 was added 1-bromo-2-chloroethane, warmed to 40°C for 18h. C): The chloroethyl derivative
 was dissolved in anhydrous dimethylsulfoxide, treated with 1,8-diazabicyclo[5.4.0]undec-7-
 ene and N,N-dimethyl-N-[(2*R*)-morpholin-2-ylmethyl]amine derivative. The crude reaction
 25 product was purified by semi-prep RPHPLC eluting with water/acetonitrile/trifluoroacetic
 acid mixtures. 604 (M+H).

Example 269

- 170 -

2-(1-benzothien-3-ylmethyl)-7-isobutyl-3-(1-methyl-1H-pyrrol-2-yl)-5-(2-piperidin-1-ylethyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione

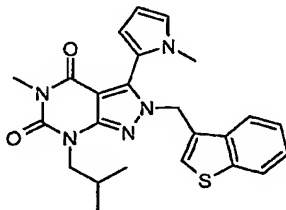


- 5 This compound was made following the procedure described above, alkylating with 1-(2-chloroethyl)piperidine hydrochloride. The crude reaction product was purified by semi-prep RP/HPLC eluting with water/acetonitrile/trifluoroacetic acid mixtures. 544 (M+H).

Example 270

10

2-(1-benzothien-3-ylmethyl)-7-isobutyl-5-methyl-3-(1-methyl-1H-pyrrol-2-yl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione



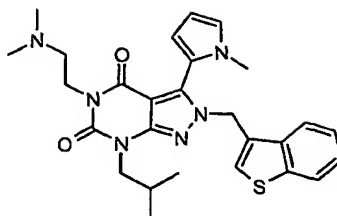
- This compound was made following the procedure described above, starting with 6-
15 hydrazino-1-isobutyl-3-methylpyrimidine-2,4(1H,3H)-dione, and condensing first with 1-benzothiophene-3-carbaldehyde, followed by 1-methyl-1H-pyrrole-2-carbaldehyde. 447 (M+H).

Example 271

20

2-(1-benzothien-3-ylmethyl)-5-[2-(dimethylamino)ethyl]-7-isobutyl-3-(1-methyl-1H-pyrrol-2-yl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione

- 171 -

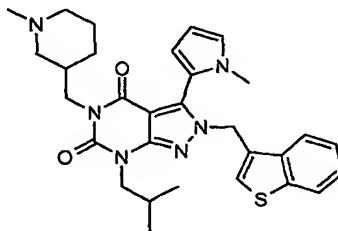


This compound was made following the procedure described above, alkylating with 2-dimethylaminoethyl chloride hydrochloride. The crude reaction product was purified by semi-prep RPHPLC eluting with water/acetonitrile/trifluoroacetic acid mixtures. 505 (M+H).

5

Example 272

2-(1-benzothien-3-ylmethyl)-7-isobutyl-5-[(1-methylpiperidin-3-yl)methyl]-3-(1-methyl-1H-pyrrol-2-yl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione



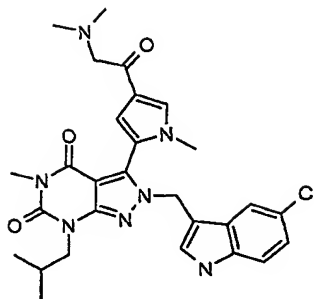
10

This compound was made following the procedure described above, alkylating with 3-chloromethyl-1-methylpiperidine hydrochloride. The crude reaction product was purified by semi-prep RPHPLC eluting with water/acetonitrile/trifluoroacetic acid mixtures. 545 (M+H).

15 **Example 273**

2-[(5-chloro-1H-indol-3-yl)methyl]-3-{4-[(dimethylamino)acetyl]-1-methyl-1H-pyrrol-2-yl}-7-isobutyl-5-methyl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione

- 172 -

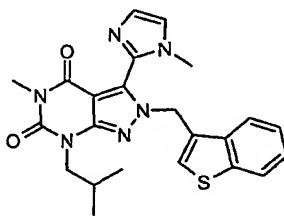


This compound was made in three steps following the procedure described above, starting with 6-hydrazino-1-isobutyl-3-methylpyrimidine-2,4(1*H*,3*H*)-dione, and condensing first 5-chloro-1*H*-indole-3-carbaldehyde, followed by 4-acetyl-1-methyl-1*H*-pyrrole-2-carbaldehyde.

- 5 To the isolated 3-(4-acetyl-1-methyl-1*H*-pyrrol-2-yl)-2-[(5-chloro-1*H*-indol-3-yl)methyl]-7-isobutyl-5-methyl-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione in anhydrous THF was added benzyltrimethylammonium dichloroiodate and heated at 65°C for 1h. The isolated chloromethyl derivative was treated with dimethylamine in *N,N*-dimethylformamide for 0.5h. The crude reaction product was purified by semi-prep RPHPLC eluting with
- 10 water/acetonitrile/trifluoroacetic acid mixtures. 550.3 (M+H).

Example 274

- 2-(1-benzothien-3-ylmethyl)-7-isobutyl-5-methyl-3-(1-methyl-1*H*-imidazol-2-yl)-2*H*-
15 pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione

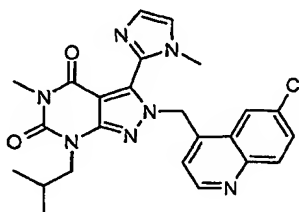


- This compound was made following the procedure described above, starting with 6-hydrazino-1-isobutyl-3-methylpyrimidine-2,4(1*H*,3*H*)-dione, and condensing first with 1-benzothiophene-3-carbaldehyde, followed by 1-methyl-1*H*-imidazole-2-carbaldehyde. 448.5
20 (M+H).

- 173 -

Example 275

2-[(6-chloroquinolin-4-yl)methyl]-7-isobutyl-5-methyl-3-(1-methyl-1H-imidazol-2-yl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione



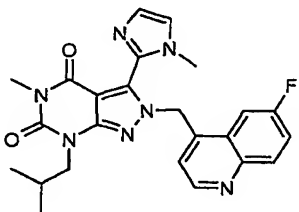
5

This compound was made following the procedure described above, starting with 6-hydrazino-1-isobutyl-3-methylpyrimidine-2,4(1*H*,3*H*)-dione, and condensing first 6-chloroquinoline-4-carbaldehyde, followed by , followed by 1-methyl-1*H*-imidazole-2-carbaldehyde. 478 (M+H).

10

Example 276

2-[(6-fluoroquinolin-4-yl)methyl]-7-isobutyl-5-methyl-3-(1-methyl-1H-imidazol-2-yl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione



15

This compound was made following the procedure described above, starting with 6-hydrazino-1-isobutyl-3-methylpyrimidine-2,4(1*H*,3*H*)-dione, and condensing first 6-fluoroquinoline-4-carbaldehyde, followed by , followed by 1-methyl-1*H*-imidazole-2-carbaldehyde. 462 (M+H).

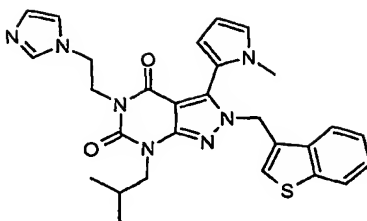
20

Example 277

2-(1-benzothien-3-ylmethyl)-5-[2-(1H-imidazol-1-yl)ethyl]-7-isobutyl-3-(1-methyl-1H-pyrrol-2-yl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione

25

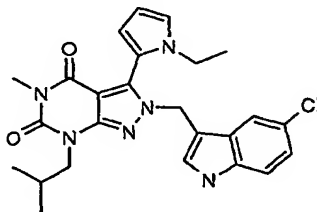
- 174 -



This compound was made following the procedure described above. The chloroethyl derivative was dissolved in anhydrous acetonitrile, treated with potassium carbonate and imidazole at 60°C. The crude reaction product was purified by semi-prep RPHPLC eluting
5 with water/acetonitrile/trifluoroacetic acid mixtures. 528 (M+H).

Example 278

2-[(5-chloro-1H-indol-3-yl)methyl]-3-(1-ethyl-1H-pyrrol-2-yl)-7-isobutyl-5-methyl-2H-
10 pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione

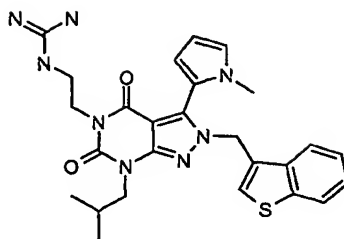


This compound was made following the procedure described above, starting with 6-hydrazino-1-isobutyl-3-methylpyrimidine-2,4(1H,3H)-dione and condensing first with 5-chloro-1H-indole-3-carbaldehyde, followed by 1-ethyl-1H-pyrrole-2-carbaldehyde. 479
15 (M+H).

Example 279

N-{2-[2-(1-benzothien-3-yl)methyl]-7-isobutyl-3-(1-methyl-1H-pyrrol-2-yl)-4,6-dioxo-
20 2,4,6,7-tetrahydro-5H-pyrazolo[3,4-d]pyrimidin-5-yl}ethyl}guanidine

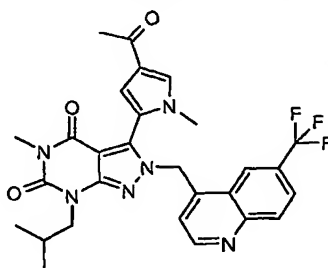
- 175 -



This compound was made following the procedure described above. The chloroethyl derivative was dissolved in anhydrous acetonitrile, treated with ammonia, followed by 1-H-Pyrazole-1-carboxamidine hydrochloride and heated for 80°C for 18h. The crude reaction product was purified by semi-prep RPHPLC eluting with water/acetonitrile/trifluoroacetic acid mixtures. 518 (M+H).

Example 280

3-(4-acetyl-1-methyl-1H-pyrrol-2-yl)-7-isobutyl-5-methyl-2-{{6-(trifluoromethyl)quinolin-4-yl}methyl}-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione



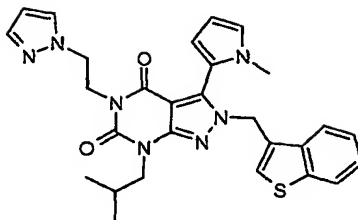
This compound was made following the procedure described above, starting with 6-hydrazino-1-isobutyl-3-methylpyrimidine-2,4(1H,3H)-dione, and condensing first with 6-trifluoromethylquinoline-4-carbaldehyde, followed by 1-methyl-4-acetyl-1H-pyrrole-2-carbaldehyde. 553(M+H).

Example 281

20

2-(1-benzothien-3-ylmethyl)-7-isobutyl-3-(1-methyl-1H-pyrrol-2-yl)-5-[2-(1H-pyrazol-1-yl)ethyl]-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione

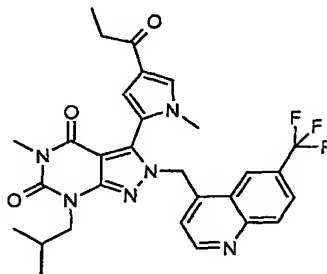
- 176 -



This compound was made following the procedure described above. The chloroethyl derivative was dissolved in anhydrous acetonitrile, treated with potassium carbonate and pyrazole. The crude reaction product was purified by semi-prep RPHPLC eluting with
 5 water/acetonitrile/trifluoroacetic acid mixtures. 528 (M+H).

Example 282

7-isobutyl-5-methyl-3-(1-methyl-4-propionyl-1H-pyrrol-2-yl)-2-{{[6-
 10 (trifluoromethyl)quinolin-4-yl]methyl}-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione

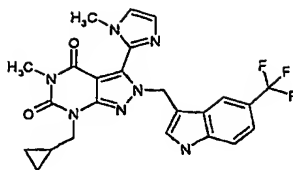


This compound was made following the procedure described above, starting with 6-hydrazino-1-isobutyl-3-methylpyrimidine-2,4(1H,3H)-dione, and condensing first with 6-trifluoromethylquinoline-4-carbaldehyde, followed by 1-methyl-4-propionyl-1H-pyrrole-2-carbaldehyde. 567(M+H).

Example 283

7-(cyclopropylmethyl)-5-methyl-3-(1-methyl-1H-imidazol-2-yl)-2-{{[5-(trifluoromethyl)-
 20 1H-indol-3-yl]methyl}-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione

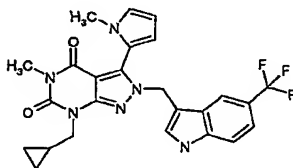
- 177 -



This compound was made following the procedure described above, starting with 1-(cyclopropylmethyl)-6-hydrazino-3-methylpyrimidine-2,4(1*H*,3*H*)-dione, and condensing
 5 first with 5-(trifluoromethyl)-1*H*-indole-3-carbaldehyde, followed by 1-methyl-1*H*-imidazole-2-carbaldehyde. 498.2 (M+H).

Example 284

10 **7-(cyclopropylmethyl)-5-methyl-3-(1-methyl-1*H*-pyrrol-2-yl)-2-{[5-(trifluoromethyl)-1*H*-indol-3-yl]methyl}-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione**

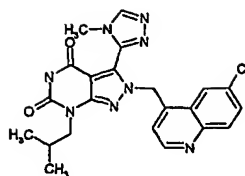


15 This compound was made following the procedure described above, starting with 1-(cyclopropylmethyl)-6-hydrazino-3-methylpyrimidine-2,4(1*H*,3*H*)-dione, and condensing first with 5-(trifluoromethyl)-1*H*-indole-3-carbaldehyde, followed by 1-methyl-1*H*-pyrrole-2-carbaldehyde. 497.2 (M+H).

20 **Example 285**

2-[(6-chloroquinolin-4-yl)methyl]-7-isobutyl-3-(4-methyl-4*H*-1,2,4-triazol-3-yl)-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione

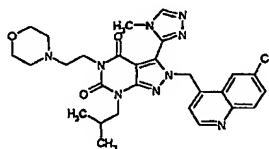
- 178 -



This compound was made following the procedure described above, starting with 6-hydrazino-1-isobutylpyrimidine-2,4(1*H*,3*H*)-dione, and condensing first with 6-chloroquinoline-4-carbaldehyde, followed by 4-methyl-4*H*-1,2,4-triazole-3-carbaldehyde. 460.2 (M+H).

Example 286

20 2-[(6-chloroquinolin-4-yl)methyl]-7-isobutyl-3-(4-methyl-4*H*-1,2,4-triazol-3-yl)-5-(2-morpholin-4-ylethyl)-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione

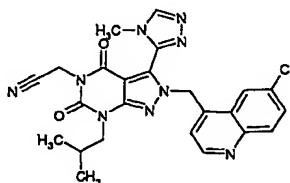


15 This compound was made by alkylation of 2-[(6-chloroquinolin-4-yl)methyl]-7-isobutyl-3-(4-methyl-4*H*-1,2,4-triazol-3-yl)-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione with 4-(2-chloroethyl)morpholine following conditions in Example 6.d. 578.2 (M+H).

Example 287

20

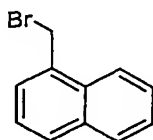
[2-[(6-chloroquinolin-4-yl)methyl]-7-isobutyl-3-(4-methyl-4*H*-1,2,4-triazol-3-yl)-4,6-dioxo-2,4,6,7-tetrahydro-5*H*-pyrazolo[3,4-*d*]pyrimidin-5-yl]acetonitrile



- 179 -

This compound was made by alkylation of 2-[(6-chloroquinolin-4-yl)methyl]-7-isobutyl-3-(4-methyl-4*H*-1,2,4-triazol-3-yl)-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione with bromoacetonitrile following conditions in Example 6.d. 504.2 (M+H).

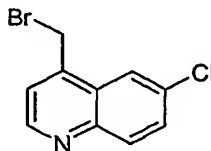
5

Example 288**1-(Bromomethyl)naphthalene**

10

1-naphthylmethanol (3.2 g) was taken up in CH₂Cl₂ (10 mL) and cooled to 0 C. Phosphorus tribromide (25 mL, 1 M in CH₂Cl₂) was added drop wise and allowed to stir at RT for 2h. Saturated sodium bicarbonate and sodium hydroxide was added slowly until alkaline. The organic layer was separated, dried over sodium sulfate, and evaporated under reduced pressure to give an off-white solid (4.4 g). Proton NMR was sufficient for the next step.

15

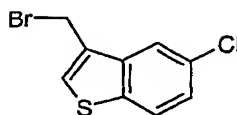
Example 289**4-(Bromomethyl)-6-chloroquinoline**

20

4-(Bromomethyl)-6-chloroquinoline was prepared from 6-chloroquinoline-4-carbaldehyde following the procedure described in the preparation of 1-(bromomethyl)naphthalene.

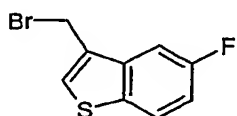
25 **Example 290****3-(Bromomethyl)-5-chloro-1-benzothiophene**

- 180 -



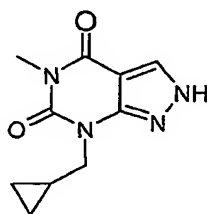
3-(Bromomethyl)-5-chloroquinoline was prepared from 5-chloro-1-benzothiophene-3-carbaldehyde following the procedure described in the preparation of 1-(bromomethyl)naphthalene.

5

Example 291**3-(Bromomethyl)-5-fluoro-1-benzothiophene**

10

3-(Bromomethyl)-5-fluoroquinoline was prepared from 5-fluoro-1-benzothiophene-3-carbaldehyde following the procedure described in the preparation of 1-(bromomethyl)naphthalene.

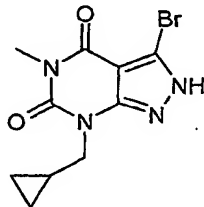
15 **Example 292****7-(Cyclopropylmethyl)-5-methyl-2H-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione**

20 1-(Cyclopropylmethyl)-6-hydrazino-3-methylpyrimidine-2,4(1*H*,3*H*)-dione (5 g) was dissolved in DMF (5mL) followed by addition of POCl₃ (4 mL) dropwise at 0 C. The reaction was warmed to 80 C for 3 h, followed by stirring at RT overnight. The solution was added to 200 mL of water and filtered to give about 5 g of yellow solids. Proton NMR was sufficient to carry on to next step.

25

Example 293**3-Bromo-7-(cyclopropylmethyl)-5-methyl-2H-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione**

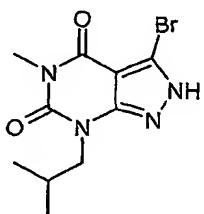
5



7-(Cyclopropylmethyl)-5-methyl-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (6.0 g), *N*-bromosuccinimide (7.8 g), and 100 mg of AIBN was taken up in 50 mL of 1,2-dichloroethane. The heterogeneous mixture was brought to reflux overnight. Water (100 mL) was added to the solution and separated. The organic layer was dried over sodium sulfate, filtered and removed under reduced pressure to give a yellow solid. The compound was flashed through a plug of silica gel, gave 6.7 g of white powder.

Example 294

15

3-Bromo-7-(isobutyl)-5-methyl-2H-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione

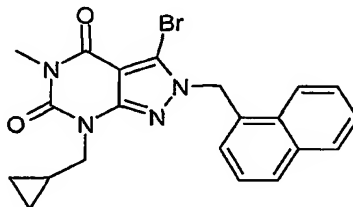
3-Bromo-7-(isobutyl)-5-methyl-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione was prepared, starting from 1-hydrazino-1-isobutyl-3-methylpyrimidine-2,4(1*H*,3*H*)-dione following the procedure described in the preparation of 3-bromo-7-(cyclopropylmethyl)-5-methyl-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione.

25

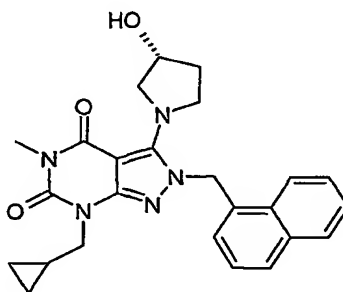
- 182 -

Example 295**3-Bromo-7-(cyclopropylmethyl)-5-methyl-2-(1-naphthylmethyl)-2H-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione**

5



3-Bromo-7-(cyclopropylmethyl)-5-methyl-2-(1-naphthylmethyl)-2H-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (6.0 g), K₂CO₃ (3.0 g), and 1-(bromomethyl)naphthalene (4.4 g) were taken up in DMF (20 mL) and heated to 70 C overnight. The mixture was extracted with ethyl acetate and water. The organic layer was separated, dried over sodium sulfate, filtered and removed under reduced pressure. The oily product was column with ethyl acetate / hexane to give a white solid (4.1 g).

Example 296**7-(Cyclopropylmethyl)-3-[(3*R*)-3-hydroxypyrrolidin-1-yl]-5-methyl-2-(1-naphthylmethyl)-2H-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione**

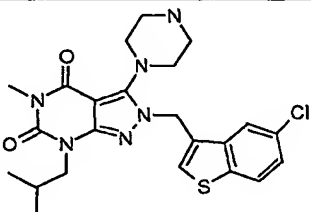
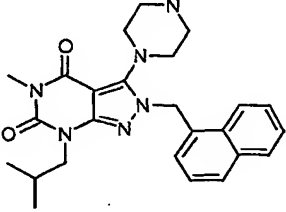
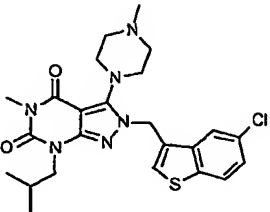
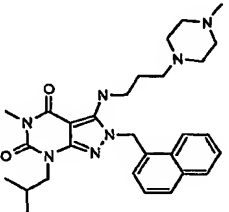
20

(3*R*)-3-Hydroxypyrrolidine (100 mg), (rac)-binap (17 mg), Pd₂(dba)₃ (13 mg) and toluene (5 mL) were combined and flushed with nitrogen for 2 min. 3-Bromo-7-(cyclopropylmethyl)-5-methyl-2-(1-naphthylmethyl)-2H-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (100 mg) was

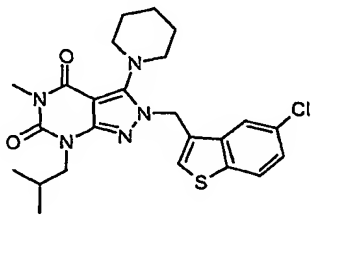
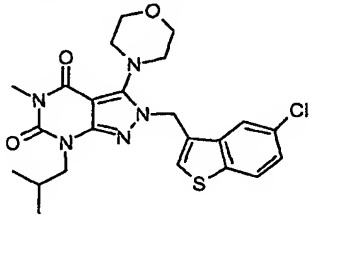
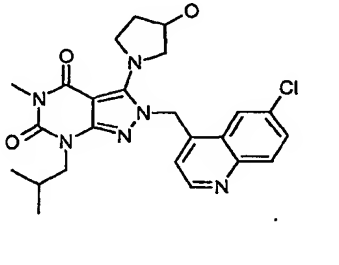
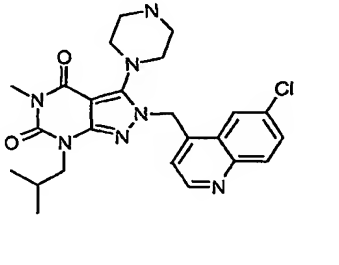
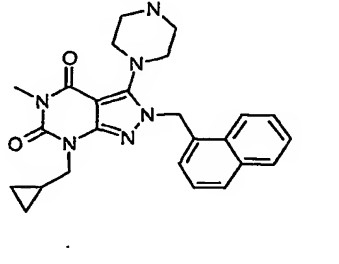
- 183 -

added and flushed with nitrogen again for 2 min, followed by addition of NaO^tBu (55 mg). The mixture was flushed with nitrogen and brought to 60 C for 8 h. Water and ethyl acetate were added and the organic layer was separated, dried over sodium sulfate, filtered, removal of solvent under reduced pressure. The oil was subjected to reverse phase chromatography
 5 using a Gilson to give 60 mg of product, ES M+H⁺ = 446.

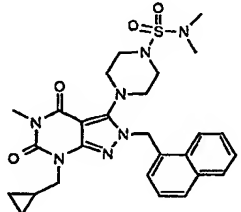
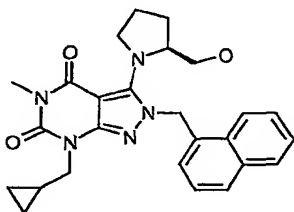
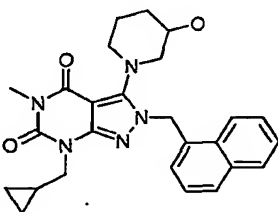
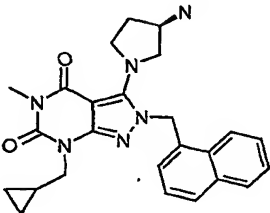
The compounds in the following Table were made using the same method as was used in the example right above.

<u>Example</u>	<u>Structure</u>	<u>Name</u>	<u>ES⁺</u> <u>(M+H)</u>
297		2-[(5-chloro-1-benzothien-3-yl)methyl]-7-isobutyl-5-methyl-3-piperazin-1-yl-2 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidine-4,6(5 <i>H</i> ,7 <i>H</i>)-dione	488
298		7-isobutyl-5-methyl-2-(1-naphthylmethyl)-3-piperazin-1-yl-2 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidine-4,6(5 <i>H</i> ,7 <i>H</i>)-dione	447
299		2-[(5-chloro-1-benzothien-3-yl)methyl]-7-isobutyl-5-methyl-3-(4-methylpiperazin-1-yl)-2 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidine-4,6(5 <i>H</i> ,7 <i>H</i>)-dione	502
300		7-isobutyl-5-methyl-3-{[3-(4-methylpiperazin-1-yl)propyl]amino}-2-(1-naphthylmethyl)-2 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidine-4,6(5 <i>H</i> ,7 <i>H</i>)-dione	518

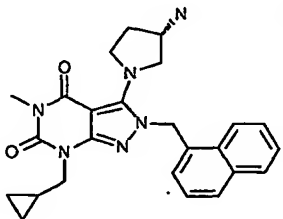
- 184 -

301		2-[(5-chloro-1-benzothiien-3-yl)methyl]-7-isobutyl-5-methyl-3-piperidin-1-yl-2 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidine-4,6(5 <i>H</i> ,7 <i>H</i>)-dione	487
302		2-[(5-chloro-1-benzothiien-3-yl)methyl]-7-isobutyl-5-methyl-3-morpholin-4-yl-2 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidine-4,6(5 <i>H</i> ,7 <i>H</i>)-dione	489
303		2-[(6-chloroquinolin-4-yl)methyl]-3-(3-hydroxypyrrolidin-1-yl)-7-isobutyl-5-methyl-2 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidine-4,6(5 <i>H</i> ,7 <i>H</i>)-dione	484
304		2-[(6-chloroquinolin-4-yl)methyl]-7-isobutyl-5-methyl-3-piperazin-1-yl-2 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidine-4,6(5 <i>H</i> ,7 <i>H</i>)-dione	483
305		7-(cyclopropylmethyl)-5-methyl-2-(1-naphthylmethyl)piperazin)-3-piperazin-1-yl-2 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidine-4,6(5 <i>H</i> ,7 <i>H</i>)-dione	445

- 185 -

306		4-[7-(cyclopropylmethyl)-5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]-N,N-dimethylpiperazine-1-sulfonamide	552
307		7-(cyclopropylmethyl)-3-[(2S)-2-(hydroxymethyl)pyrrolidin-1-yl]-5-methyl-2-(1-naphthylmethyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione	460
308		7-(cyclopropylmethyl)-3-(3-(hydroxypiperidin-1-yl))-5-methyl-2-(1-naphthylmethyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione	460
309		3-[(3S)-3-aminopyrrolidin-1-yl]-7-(cyclopropylmethyl)-5-methyl-2-(1-naphthylmethyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione	445

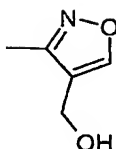
- 186 -

310	 Chiral	3-[(3 <i>R</i>)-3-aminopyrrolidin-1-yl]-7-(cyclopropylmethyl)-5-methyl-2-(1-naphthylmethyl)-2 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidine-4,6(5 <i>H</i> ,7 <i>H</i>)-dione	445
-----	---	--	-----

- 187 -

Example 311**(3-Methylisoxazol-4-yl)methanol**

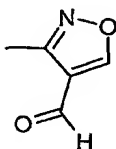
5



Ethyl-3-methylisoxazole-4-carboxylate (1.2 g) was taken up in toluene (10 mL) and cooled to -78 C. 20 mL of borane (1M in CH₂Cl₂) was added dropwise and allowed to stir for 1 hour at -78 C. The reaction was finished based on HPLC. The solution was quenched with methanol and filtered through a plug of celite. The organic solution was removed under reduced pressure gave a clear oil. The material was sufficiently clean to carry on to the next step.

Example 312

15

3-Methylisoxazole-4-carbaldehyde

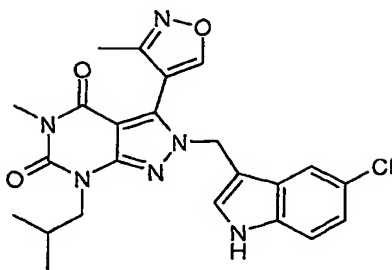
The crude material was dissolved in 25 mL of CH₂Cl₂ and pyridinium chlorochromate (PCC) (2.2 g), (20% on basic Al₂O₃) was added. The mixture was stirred overnight at RT. The heterogeneous mixture was filtered through a plug of celite. The brown solution was taken up in ethyl acetate and was column through a plug of silica gel to give clear oil.

Example 313

25

2-[(5-chloro-1*H*-indol-3-yl)methyl]-7-isobutyl-5-methyl-3-(3-methylisoxazol-4-yl)-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione

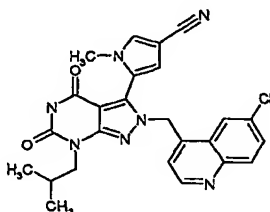
- 188 -



5-Chloro-1*H*-indole-3-carbaldehyde(3-isobutyl-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)hydrazone (100 mg) was added to a solution of isoxazolaldehyde (86mg) in dimethylformamide at RT. Piperidine (100 μ L) was then added and brought to 80 C for 8h. After cooling to RT, ethyl acetate (25 mL) was added to brown solution and water (25 mL) was added and extracted. The aqueous layer was back extract with ethyl acetate and then combined. The organic layer was dried over sodium sulfate, filtered and removal of solvent to give an amorphous solid. The isoxazole was submitted the Gilson Preparatory chromatography to give a 100 mg of white solids. ES $M+H^+$ 467.

Example 314

5-{2-[(6-chloroquinolin-4-yl)methyl]-7-isobutyl-4,6-dioxo-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-1-methyl-1*H*-pyrrole-3-carbonitrile



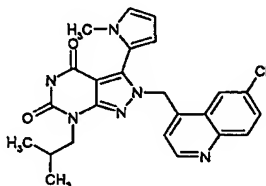
20 This compound was made following the procedure described above, starting with 6-hydrazino-1-isobutylpyrimidine-2,4(1*H*,3*H*)-dione, and condensing first with 6-chloroquinoline-4-carbaldehyde, followed by 5-formyl-1-methyl-1*H*-pyrrole-3-carbonitrile. ES $M+H^+$ = 463.

- 189 -

Example 315

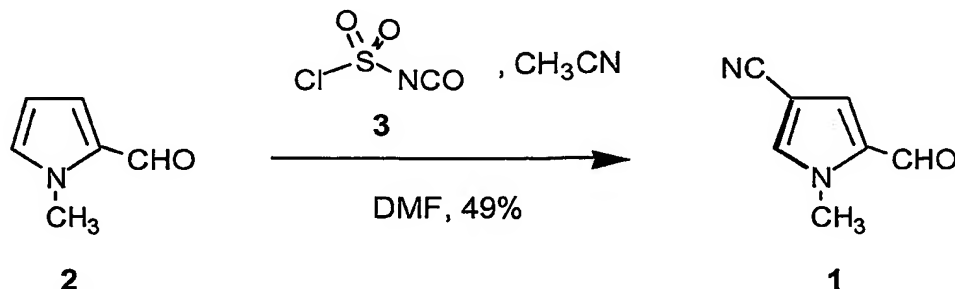
2-[(6-chloroquinolin-4-yl)methyl]-7-isobutyl-3-(1-methyl-1*H*-pyrrol-2-yl)-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione

5



This compound was made following the procedure described above, starting with 6-hydrazino-1-isobutylpyrimidine-2,4(1*H*,3*H*)-dione, and condensing first with 6-chloroquinoline-4-carbaldehyde, followed by 1-methyl-2-pyrrolicarboxaldehyde. ES $M+H^+$ = 488.

The remaining numbered examples contain intermediates that are used to make the compounds described the previous examples.

Examples 316

4-Cyano-1-methylpyrrole-2-carboxaldehyde (1): To a solution of **2** (19.70 g, 0.18 mol) in acetonitrile at -60°C, **3** (47.5 mL, 0.50 mol) was added dropwise and the reaction mixture was warmed to room temperature overnight, cooled to 0°C, added DMF (70 mL, 0.90 mol) and heated at 55 °C for 1h. The reaction mixture was then poured on an ice-cold solution of 2N aq. NaOH (500 mL) and extracted with EtOAc. The organic extracts were dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude product was purified by flash

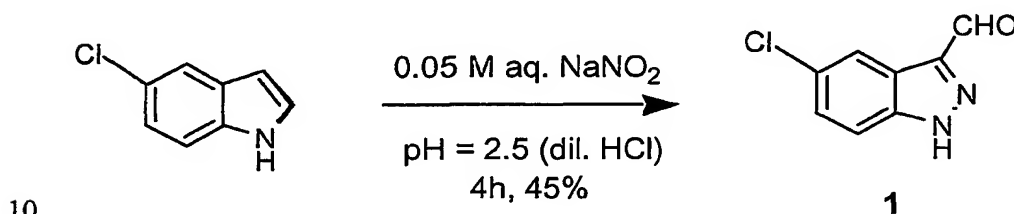
25

- 190 -

chromatography using 10-20% gradients of EtOAc/hexanes as eluent. Further purification was done by crystallization (EtOAc/hexanes) to obtain **1** (11.74 g, 49% yield) as a white solid. Mp 125-126°C (lit.¹ 123-124 °C). ¹H NMR (300 MHz, CDCl₃): δ 9.62 (s, 1H), 7.31 (s, 1H), 7.18 (d, 1.7 Hz, 1H), 4.01 (s, 3H). Analysis calcd. for C₇H₆N₂O; C, 62.68; H, 4.51; N, 20.88; found, C, 62.92; H, 4.45; N, 20.92.¹

Ref: 1. Loader, C. E.; Anderson, H. J. *Can. J. Chem.* **1981**, 59, 2673.

2. Sonnet, P. E. *J. Heterocycl. Chem.* **1973**, 10, 113.

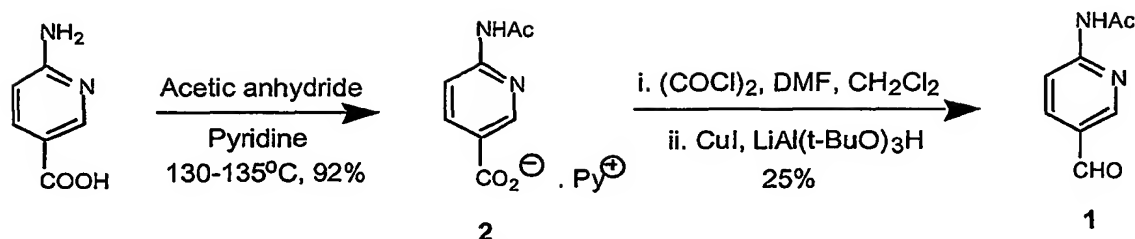


Examples 317

5-Chloro-1H-indazole-3-carboxaldehyde (1): A mixture of 5-chloroindole (6.04 g, 39.8 mmol) and 0.05 M aq. sodium nitrite (8 L, adjusted to pH 2.5 with dilute HCl) was stirred at room temperature for 4h. The precipitated solid was removed by filtration and the filtrate was extracted with EtOAc (2 L). The organic extracts were washed with brine, dried over Na₂SO₄, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel with 10-15% EtOAc/hexanes gradient to give **1** (3.23 g, 45% yield) as an off-white solid. Mp 213-214°C (lit.¹ 209-210 °C, dec). ¹H NMR (300 MHz, CD₃CN): δ 10.17 (s, 1H), 8.18 (d, 1.9 Hz, 1H), 7.65 (dd, 8.8, 0.5 Hz, 1H), 7.47 (dd, 8.8, 2.2 Hz, 1H). MS m/z: 181 (M+1). Analysis calcd. for C₈H₅ClN₂O; C, 53.21; H, 2.79; N, 15.51; Cl, 19.63; found, C, 53.31; H, 2.80; N, 15.55; Cl, 19.75.¹

Ref: 1. Buchi, G.; Lee, G. C. M.; Yang, D.; Tannenbaum, S. R. *J. Am. Chem. Soc.* **1986**, 108(14), 4115-4119.

- 191 -

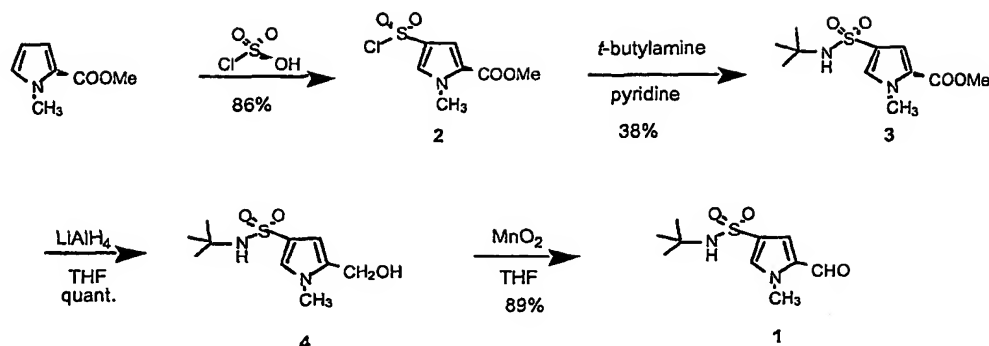
**Examples 318**

2-(N-acetylamido)pyridine-5-carboxylic acid pyridine salt (2): A mixture of 6-aminonicotinic acid (15.1 g, 109.1 mmol), acetic anhydride (12.4 mL, 131.4 mmol), and pyridine (450 mL) was heated at 130-135°C for 24h. The mixture was diluted with hexanes after cooling to room temperature, the precipitated solid 2 (26.0 g, 92%) was filtered, and dried in vacuo. ¹H NMR (300 MHz, DMSO-d₆): δ 10.86 (bs, 1H), 8.81 (m, 1H), 8.58 (m, 2H), 8.24 (dd, 8.8, 2.2 Hz, 1H), 8.17 (d, 8.8 Hz, 2H), 7.79 (ttd, 7.7, 1.7, 0.5 Hz, 1H), 7.39 (m, 2H), 2.14 (s, 3H).

Examples 319

2-(N-acetylamido)pyridine-5-carboxaldehyde (1): To a solution of DMF (7.75 mL, 100 mmol) in dry CH₂Cl₂ (80 mL) cooled to 0°C, oxalyl chloride (26.0 mL, 298 mmol) was added dropwise. After 1h excess solvent was stripped off and was replaced by acetonitrile (150 mL) and THF (200 mL). A suspension of 2 (26.0 g, 100 mmol) in THF was then added to the reaction flask at -30°C and was allowed to stir for 1h. The mixture was further cooled to -78°C and CuI (1.94 g, 10.2 mmol) was added followed by a rapid addition of lithium tri-tert-butoxyaluminumhydride (200 mL, 1.0 M solution in THF). After 20 min. the reaction was quenched with 2N aq. HCl, warmed to room temperature and extracted with EtOAc (1 L). The organic extracts were dried over Na₂SO₄, filtered, and concentrated. The crude product was purified by flash chromatography using 15-40% gradients of EtOAc/hexanes as eluent. Pure 1 (4.08 g, 25% yield) was obtained as a white solid by crystallization from hot EtOAc. Mp 152-153°C. ¹H NMR (300 MHz, CDCl₃): δ 10.99 (s, 1H), 9.96 (s, 1H), 8.85 (dd, 2.2, 0.8 Hz, 1H), 8.26 (bd, 8.8 Hz, 1H), 8.21 (dd, 8.8, 2.2 Hz, 1H), 2.12 (s, 3H). MS m/z: 165 (M+1). Analysis calcd. for C₈H₈N₂O₂; C, 58.53; H, 4.91, N, 17.06; found, C, 58.25; H, 4.81; N, 16.80.

- 192 -

**Examples 320**

5

Methyl (4-chlorosulfamoyl-N-methylpyrrole)-2-carboxylate (2): Methyl N-methylpyrrole-2-carboxylate (9.83 g, 70.69 mmol) was added dropwise to chlorosulfonic acid (50 mL) at 0°C under nitrogen atmosphere. The reaction mixture was then warmed to room temperature overnight. Work up was done by slow addition to ice cold water, followed by extraction with CH_2Cl_2 . The combined organic extracts were dried over Na_2SO_4 , filtered, and concentrated to give 2 (13.77, 86%) as a white solid. ^1H NMR (300 MHz, CDCl_3): δ 7.48 (d, 1.9 Hz, 1H), 7.37 (d, 1.9 Hz, 1H), 4.01 (s, 3H), 3.87 (s, 3H).

Examples 321

15

Methyl (4-*tert*-butylsulfamoyl-N-methylpyrrole)-2-carboxylate (3): A premixed solution of butylamine (7.75 mL, 73.74 mmol) in pyridine was added slowly to a mixture of 2 (15.43 g, 68.38 mmol) in pyridine (80 mL) at 0°C under nitrogen atmosphere. The reaction was allowed to warm to room temperature and stirred for 3h. The mixture was then poured into H_2O (300mL), extracted with EtOAc, the extracts were washed with brine, dried over Na_2SO_4 , filtered, and concentrated. The crude product was purified by flash chromatography over silica gel using 10-25% EtOAc/hexanes gradient as eluent to give 3 (18.76 g, 38% yield) as a white solid. ^1H NMR (300 MHz, CDCl_3): δ 7.25 (d, 1.9 Hz, 1H), 7.17 (d, 1.9 Hz, 1H), 4.63 (bs, 1H), 3.97 (s, 3H), 3.84 (s, 3H), 1.27 (s, 9H). MS m/z : 274 ($M-1$).

25

Examples 322

- 193 -

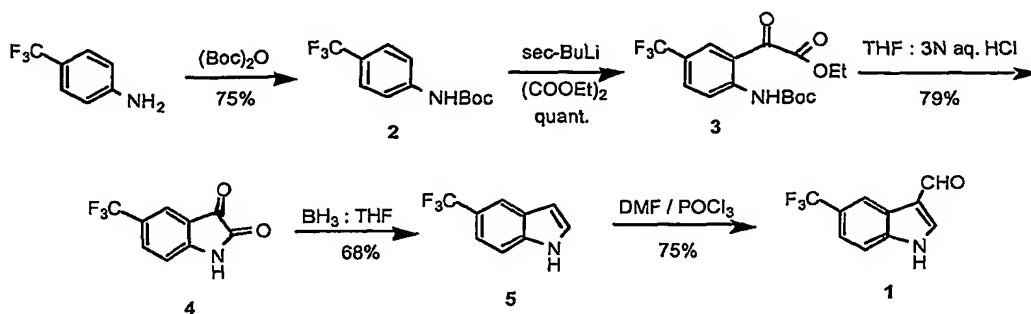
4-tert-Butylsulfamoyl-N-methylpyrrole-2-methanol (4): A solution of 3 (7.12 g, 25.95 mmol) in dry THF (120 mL) at -78°C under nitrogen was charged with LiAlH₄ (30 mL, 1.0 M solution in THF). The reaction mixture was warmed to 10°C and stirred for 2h. The mixture was poured onto EtOAc:H₂O (1:1, 300 mL), saturated with NaCl, extracted with EtOAc. The organic extracts were dried over Na₂SO₄, filtered, and concentrated to give 4 (6.40 g, quant.) as a white solid. ¹H NMR (300 MHz, CDCl₃): δ 7.11 (d, 1.9 Hz, 1H), 6.35 (d, 1.9 Hz, 1H), 4.64 (s, 1H), 4.54 (d, 5.5 Hz, 2H), 3.68 (s, 3H), 2.18 (t, 5.5 Hz, 1H), 1.24 (s, 9H).

Examples 323

10

4-tert-Butylsulfamoyl-N-methylpyrrole-2-carboxaldehyde (1): A solution of 4 (6.40 g, 25.98 mmol) in dry THF (750 mL) under nitrogen was charged with MnO₂ (65.0 g, 0.64 mol) and was allowed to stir at room temperature for 1h. The mixture was filtered through celite; the filtrate was concentrated. Purification by flash chromatography on silica gel using 10-25% EtOAc/hexanes gradient as eluent afforded 1 (5.67 g, 89%) as a white solid. Mp 97-98 °C. ¹H NMR (300 MHz, CDCl₃): δ 9.95(d, 0.8 Hz, 1H), 7.33 (bs, 1H), 7.18 (d, 1.9 Hz, 1H), 4.69 (bs, 1H), 3.97 (s, 3H), 1.27 (s, 9H). MS m/z: 243 (M-1). Analysis calcd. for C₁₀H₁₆N₂O₃S; C, 49.16; H, 6.60, N, 11.47; found, C, 48.99; H, 6.70; N, 11.45.

20 **Ref:** Mornata, C.; Molins-Pujol, A. M.; Pujol, M. D.; Bonal, J. *J. Chem. Soc. Perkin Trans. 1* 1998, 19, 3285-3291.



25

Examples 324

- 194 -

4-Trifluoromethyl-carbamic acid *tert*-butyl ester (2): A mixture of 4-trifluoromethyl aniline (7.8 mL, 62.1 mmol) and di-*tert*-butyl-dicarbonate (15.0 g, 68.9 mmol) was refluxed for 12h under nitrogen atmosphere. The mixture was concentrated in vacuo. The crude product was purified by flash chromatography on silica gel using 10% EtOAc/hexanes as eluent to give **2** (12.2 g, 75% yield) as a white solid. ¹H NMR (300 MHz, CDCl₃): δ 7.54 (d, 8.6 Hz, 2H), 7.47 (d, 8.6 Hz, 2H), 6.63 (bs, 1H), 1.52 (s, 9H). MS m/z: 260 (M-1).

Examples 325

Ethyl-2-(2-N-Boc-5-trifluoromethylphenyl)-2-oxo-carboxylate (3): A solution of **2** (5.24 g, 20.06 mmol) in dry THF (50 mL) was charged with sec-butyllithium (38 mL, 49.40 mmol, 1.3 M in cyclohexane) at -40°C under nitrogen atmosphere. The mixture was further cooled to -78°C and diethyloxalate (3.3 mL, 24.3 mmol) was added and allowed to stir for 1h. The reaction was quenched with 1N HCl (60 mL), warmed to room temperature, extracted with ether, the extracts were dried over MgSO₄, filtered, and concentrated to give **3** (7.24 g, quant. yield) as a yellow oil. ¹H NMR (300 MHz, CDCl₃): δ 10.56 (bs, 1H), 8.70 (d, 9.1 Hz, 1H), 7.96 (dd, 1.7, 0.8 Hz, 1H), 7.80 (m, 1H), 4.49 (q, 7.1 Hz, 2H) 1.45 (s, 9H), 1.29 (t, 7.1 Hz, 3H). MS m/z: 360 (M-1).

Examples 326

5-Trifluoromethyl-1H-indole-2,3-dione (4): A mixture of **3** (7.24 g, 20.06 mmol), THF (60 mL), and 3N HCl (60 mL) was refluxed for 3 h. The mixture was extracted with EtOAc (3x75 mL), the extracts were washed with brine, dried over MgSO₄, and concentrated. Purification of the crude product by flash chromatography on silica gel using 2% MeOH/CHCl₃ as eluent afforded **4** (3.41 g, 79% yield) as a yellow orange solid. ¹H NMR (300 MHz, DMSO-d₆): δ 7.92 (dd, 8.2, 1.9 Hz, 1H), 7.80 (s, 1H), 7.07 (d, 8.2 Hz, 1H).

Examples 327

30

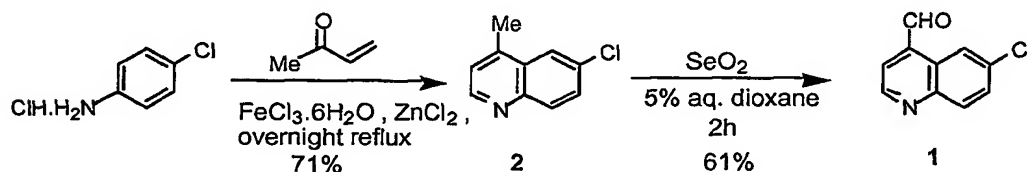
5-Trifluoromethyl-1H-indole (5): To a solution of **4** (6.75 g, 31.38 mmol) in dry THF (200 mL) at 0°C under nitrogen atmosphere BH₃.THF solution (82 mL, 1 M in THF) was added dropwise. The mixture was allowed to warm to room temperature and stirred for 1h. The

- 195 -

reaction was quenched with 6N ice-cold aq. HCl (30 mL), made alkaline (pH 7-8) with 2 N NaOH, saturated with NaCl, extracted with EtOAc, the extracts were dried (MgSO₄), concentrated. Purification by chromatography on silica gel using CH₂Cl₂ as eluent afforded 5 (3.95 g, 68% yield) as an off white solid. ¹H NMR (300 MHz, MeOH-d₄): δ 7.87 (m, 1H), 7.51 (dd, 8.5, 0.8 Hz, 1H), 7.47 (d, 8.5 Hz, 1H), 7.37 (d, 3.2 Hz, 1H), 7.34 (dd, 8.5, 1.6 Hz, 1H), 6.57 (dd, 3.2, 0.8 Hz, 1H). MS m/z: 184 (M-1).

Examples 328

- 10 **5-Trifluoromethyl-1*H*-indole-3-carbaldehyde (1):** Phosphorous oxychloride (7.6 mL, 83.0 mmol) was added dropwise to DMF (150 mL) at 0°C. A solution of 5 (4.5 g, 24.4 mmol) in DMF (30 mL) was added after 15 min. and the reaction mixture was allowed to warm to room temperature for 2h. The mixture was poured on ice-water (300 g), made alkaline (pH 7-8) with 2 N aq. NaOH, extracted with EtOAc, the extracts were washed with brine, dried (MgSO₄), and concentrated. The crude product was purified by flash chromatography on silica gel using 10% MeOH/CHCl₃ as eluent. Recrystallization by dissolving yellow solid in hot MeOH and pouring onto cold water afforded 1 (3.9 g, 75% yield) as a white solid. Mp 242-243°C. ¹H NMR (300 MHz, MeOH-d₄): δ 9.95 (s, 1H), 8.48 (bs, 1H), 8.22 (s, 1H), 7.63 (d, 8.5 Hz, 1H), 7.53 (dd, 8.5, 1.7 Hz, 1H). MS m/z: 212 (M-1). Analysis calcd. for C₁₀H₆NOF₃; C, 56.35; H, 2.84, N, 6.57; found, C, 56.60; H, 2.92; N, 6.55.

**Examples 329**

6-Chloro-4-methyl-quinoline (2): A 3 neck round bottom flask equipped with reflux condenser and stirrer was charged with 4-chloro-aniline.HCl salt (26.2 g, 160 mmol), FeCl₃·6H₂O

- 196 -

(69.1 g, 256 mmol), and ZnCl_2 (2.54g, 18.7 mmol) in 95% EtOH (200 mL) under N_2 atmosphere. The reaction mixture was heated to an internal temperature of 60°C after which methylvinylketone (10.6 mL, 128 mmol) was added dropwise over 1h. The mixture was refluxed overnight. The solvent was removed in vacuo and the black slurry was made
5 alkaline with 25% aq. NaOH (400 mL). The product was extracted with ethyl acetate till no more florescence to the organic layer on TLC was observed. The combined organic extracts were dried over MgSO_4 , filtered, and concentrated. Purification of the crude product by flash chromatography using 30% EtOAc / hexanes as eluent gave **2** (16.0 g, 71% yield) as a light brown solid. ^1H NMR (300 MHz, CDCl_3): δ 8.77 (d, 3.6 Hz, 1H), 8.04 (d, 9.1 Hz, 1H), 7.97
10 (d, 2.2 Hz, 1H), 7.64 (dd, 9.1, 2.2 Hz, 1H), 7.26 (dd, 3.6, 0.8 Hz, 1H), 2.68 (s, 3H).¹

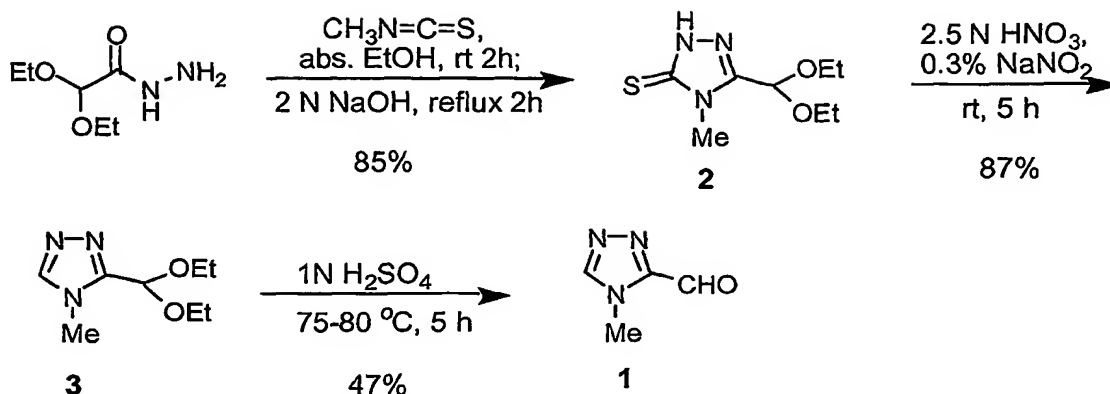
Examples 330

6-Chloro-quinoline-4-carbaldehyde (1): A solution of **2** (16.04 g, 90.6 mmol) and SeO_2
15 (13.0 g, 117.3 mmol) in 5% aq. 1,4-dioxane (200 mL) was refluxed for 2h. The precipitated selenium was filtered off and the filtrate was evaporated to dryness in vacuo. The residue was taken into CH_2Cl_2 , and filtered through a short plug of silica gel. The filtrate was concentrated to give a light brown solid. Further purification by crystallization (EtOAc/Hexanes) gave **1** (11.6 g, 61%) as a pale yellow solid. Mp $152\text{--}153^\circ\text{C}$ (lit.² $153\text{--}154$
20 $^\circ\text{C}$). ^1H NMR (300 MHz, CDCl_3): δ 10.43 (s, 1H), 9.20 (d, 4.4 Hz, 1H), 9.10 (d, 2.2 Hz, 1H), 8.16 (d, 9.1 Hz, 1H), 7.82 (d, 4.4 Hz, 1H), 7.77 (dd, 9.1, 2.2 Hz, 1H). MS m/z: 192 (M+1). Analysis calcd. for $\text{C}_{10}\text{H}_6\text{ClNO}$; C, 62.68; H, 3.16; N, 7.31; Cl, 18.50; found, C, 62.92; H, 3.33; N, 7.23; Cl, 18.60.²

25 **Ref:** 1. Campbell, K. N.; Sommers, A. H.; Kerwin, J. F.; Campbell, B. K. *J. Am. Chem. Soc.* **1945**, 67, 86-89.

2. Jones, D. H.; Slack, R.; Squires, S.; Wooldridge, K. R. H. *J. Med. Chem.* **1965**, 8, 676-680.

- 197 -

**Examples 331**

- 5 **5-Diethoxymethyl-4-methyl-2,4-dihydro-[1,2,4]triazole-3-thione (2):** A mixture of diethoxyacetic acid hydrazide¹ (13.36 g, 82.5 mmol) and methyl isocyanate (5.57 mL, 82.0 mmol) in absolute EtOH (100 mL) was allowed to stir at room temperature under N₂ atmosphere. After 2h 2N aq. NaOH (150 mL) was added and the reaction mixture was refluxed for 2h. The reaction mixture was then cooled to 0°C and acidified with 6 N HCl (35 mL). The resulting solution was then extracted with CH₂Cl₂ (3x150 mL), dried over MgSO₄, filtered and concentrated to give 2 (15.15 g, 85% yield) as a yellow oil. ¹H NMR (300 MHz, CDCl₃): δ 5.39 (s, 1H), 3.72 (m, 2H), 3.67 (s, 3H), 3.56 (m, 2H), 1.25 (t, 7.1 Hz, 6H).²
- 10

Examples 332

15

- 5-Diethoxymethyl-4-methyl-4H-[1,2,4]triazole (3):** A solution of NaNO₂ (0.4 g, 5.7 mmol) in 2.5 N aq. HNO₃ (150 mL) was added to 2 (15.15, 70.5 mmol) at 0°C in a dropwise manner over 1h with constant stirring. The reaction mixture was warmed to room temperature and stirred for 4h (monitored by TLC), then cooled to 0°C and neutralized with 10 N NaOH. The resulting solution was extracted with CH₂Cl₂ (3x150 mL), dried over MgSO₄, filtered, and concentrated in vacuo to give 3 (11.3 g, 87%) as a yellow oil. ¹H NMR (300 MHz, CDCl₃): δ 8.04 (s, 1H), 5.67 (s, 1H), 3.79 (m, 2H), 3.78 (s, 3H), 3.56 (m, 2H), 1.25 (t, 7.1 Hz, 6H).²
- 20

Examples 333

25

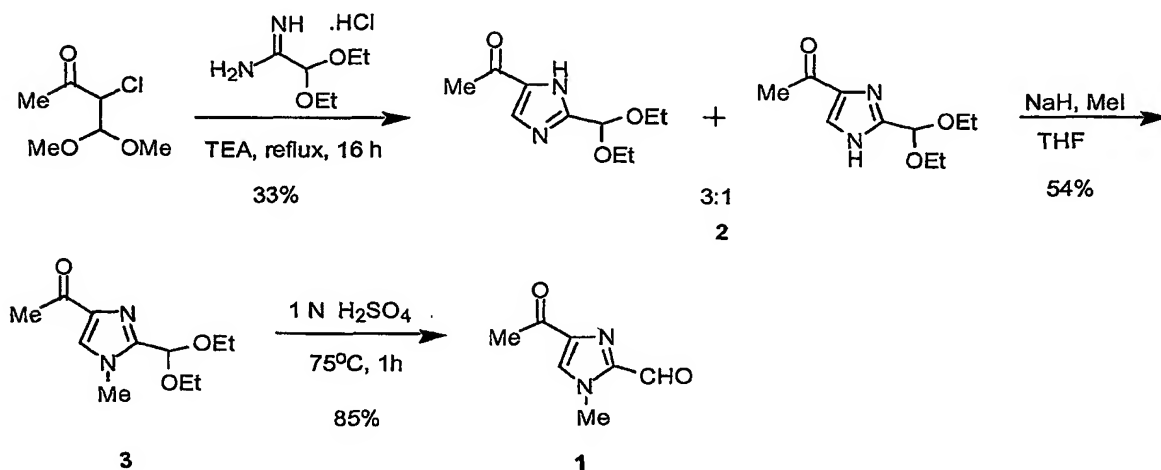
- 198 -

4-Methyl-4H-[1,2,4]triazole-3-carbaldehyde (1): A solution of **3** (11.4 g, 61.3 mmol) in 1N aq. H_2SO_4 (240 mL) was heated at 70-75°C for 4h (monitored by TLC). The mixture was cooled to 0°C and neutralized with solid NaHCO_3 . The resulting solution was saturated with NaCl and extracted with t-BuOH: CH_2Cl_2 (38:62, 3x150 mL). The combined organic extracts were dried over MgSO_4 , filtered and concentrated. The residue obtained was purified by chromatography using 5% MeOH/ CHCl_3 as an eluent to give **1** (3.21 g, 47% yield) as a white solid. Mp 101-102°C (lit.² 103-104°C); ^1H NMR (300 MHz, CDCl_3): δ 10.15 (s, 1H), 8.27 (s, 1H), 4.01 (s, 3H). MS m/z: 112 (M+1). Analysis calcd. for $\text{C}_4\text{H}_5\text{N}_3\text{O}$; C, 43.24; H, 4.54; N, 37.82; found, C, 43.39; H, 4.61; N, 37.60.²

10

Ref: 1. Khorshidi, H. S.; Rodrigez, A. C.; *Nucleosides Nucleotides* **1994**, 13, 1809-1818.

2. Moderhack, D.; Hoppe-Tichy, T. *J. Prakt. Chem.* **1996**, 338, 169.171.



15

3**1**

Examples 334

1-(2-Diethoxymethyl-3H-imidazole-4-yl)-ethanone (2): A mixture of 3-chloro-4,4-dimethoxy butan-2-one¹ (7.27g, 43.5 mmol), diethoxyacetamidine.HCl salt² (18.2 g, 100 mmol) and triethylamine (30.0 mL, 216 mmol) in dry THF (200 mL) was refluxed for 60 h (monitored by ^1H NMR) under N_2 atmosphere. The mixture was then filtered through celite, washed with ethyl acetate, and concentrated. The crude product was purified by flash chromatography on silica gel with 40-60% EtOAc/hexanes gradient to give **2** (3.01 g, 33%)

20

- 199 -

yield) as a yellow solid. ^1H NMR (300 MHz, CDCl_3), 3:1 mixture of 1H:3H isomers: δ 10.05 (bs, 1H), 7.70, 7.67 (2s, 1H), 5.61, 5.59 (2s, 1H), 3.63 (m, 4H), 2.57 (2s, 3H), 1.25 (2t, 7.1 Hz, 6H). MS m/z : 213 (M+1, 20%), 167 (-EtOH, 100%).

5 Examples 335

1-(2-Diethoxymethyl-3-methyl-imidazole-4-yl)-ethanone (3): To a suspension of NaH (993 mg, 24.8 mmol, 60% suspension in mineral oil, washed with pentane) in THF (25 mL) at 0°C under N_2 atmosphere was added a solution of 2 (3.51g, 16.6 mmol) in THF (40 mL) in a dropwise manner over 30 min. Methyl iodide (1.13 mL, 18.2 mmol) was added after 20 min and the reaction mixture was allowed to warm to room temperature and stirred for 4h (monitored by TLC). The mixture was then cooled back to 0°C , quenched by adding sat. NH_4Cl , diluted with CHCl_3 (200 mL), filtered through celite, and the filtrate was concentrated. The crude product was purified by flash chromatography on silica gel with 40-60% EtOAc/hexanes gradient to give 3 (2.0 g, 54%) as a colorless oil. ^1H NMR (300 MHz, CDCl_3): δ 7.51 (s, 1H), 5.49 (s, 1H), 3.82 (s, 3H), 3.77 (m, 2H), 3.56 (m, 2H) 2.51 (s, 3H), 1.24 (t, 7.1 Hz, 3H). MS m/z : 227 (M+1, 100%), 181 (-EtOH, 80%).

Examples 336

20

1-(2-carbaldehyde-imidazole-4-yl)-ethanone (1): The compound 3 (2.49g, 11.0 mmol) was dissolved in 1N H_2SO_4 (20 mL) and was heated at $75\text{--}80^\circ\text{C}$ for 1h (monitored by TLC). The reaction mixture was cooled to 0°C , quenched with solid NaHCO_3 , extracted with CHCl_3 (3x75 mL), dried over MgSO_4 , and concentrated. The crude product was purified by flash chromatography on silica gel with 40-50% EtOAc/hexanes gradient to give 1 (1.43 g, 85% yield) as a white solid. Mp $162\text{--}163^\circ\text{C}$. ^1H NMR (300 MHz, CDCl_3): δ 9.85 (d, 0.8 Hz, 1H), 7.69 (s, 1H), 4.05 (s, 3H), 2.59 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3): δ 194.0, 182.4, 143.1, 142.9, 129.6, 35.7, 26.4. MS m/z : 153 (M+1).). Analysis calcd. for $\text{C}_7\text{H}_8\text{N}_2\text{O}_2$; C, 55.26; H, 5.30; N, 18.41; found, C, 55.50; H, 5.42; N, 18.49.

30

Ref: 1. Reiter, L. A. *J. Org. Chem.* **1984**, 49(19), 3494-3498

2. Schaefer, F. C.; Peters, G.A. *J. Org. Chem.* **1961**, 26, 412-418.

- 200 -

Other compounds that have been made by the above procedures are:

- (5-{2-[(1-benzyl-1H-indol-3-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl}-2-furyl)methyl acetate,
- (5-{2-[(4'-fluoro-1,1'-biphenyl-2-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl}-2-furyl)methyl acetate,
- 5 (5-{2-[2-(benzyloxy)benzyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl}-2-furyl)methyl acetate,
- (5-{7-isobutyl-2-[3-(4-methoxyphenoxy)benzyl]-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl}-2-furyl)methyl acetate,
- 10 (5-{7-isobutyl-5-methyl-2-[(1-methyl-1H-indol-3-yl)methyl]-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl}-2-furyl)methyl acetate,
- (5-{7-isobutyl-5-methyl-2-[(2Z)-5-methyl-2-phenyl-2-hexenyl]-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl}-2-furyl)methyl acetate,
- (5-{7-isobutyl-5-methyl-4,6-dioxo-2-[(2Z)-2-phenyl-2-pentenyl]-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl}-2-furyl)methyl acetate,
- 15 (5-{7-isobutyl-5-methyl-4,6-dioxo-2-[(3-phenyl-1H-pyrazol-4-yl)methyl]-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl}-2-furyl)methyl acetate,
- [5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-3-(4-pyridinyl)-2,4,5,6-tetrahydro-7H-pyrazolo[3,4-d]pyrimidin-7-yl]acetonitrile,
- 20 [5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-3-(4-pyridinyl)-2,4,5,6-tetrahydro-7H-pyrazolo[3,4-d]pyrimidin-7-yl]acetic acid,
- 2-(1-benzothien-3-ylmethyl)-3-[3-(2-hydroxyethoxy)phenyl]-7-isobutyl-5-methyl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
- 2-(1-benzothien-3-ylmethyl)-3-cyclohexyl-7-isobutyl-5-methyl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
- 25 2-(1-benzothien-3-ylmethyl)-7-isobutyl-5-methyl-3-(1-methyl-1H-imidazol-2-yl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
- 2-(1-benzothien-3-ylmethyl)-7-isobutyl-5-methyl-3-(1-methyl-1H-pyrrol-2-yl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
- 30 2-(1-benzothien-3-ylmethyl)-7-isobutyl-5-methyl-3-(4-methyl-1H-imidazol-5-yl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
- 2-(1H-indol-4-ylmethyl)-7-isobutyl-5-methyl-3-(4-pyridinyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,

- 201 -

- 2-(1H-indol-7-ylmethyl)-7-isobutyl-5-methyl-3-(4-pyridinyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
2-(2,3-dichlorobenzyl)-3-[3-(2-hydroxyethoxy)phenyl]-7-isobutyl-5-methyl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
5 2-(2,3-dichlorobenzyl)-7-isobutyl-3,5-dimethyl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
2-(2,3-dichlorobenzyl)-7-isobutyl-5-methyl-3-(1-methyl-1H-imidazol-2-yl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
2-(2,3-dichlorobenzyl)-7-isobutyl-5-methyl-3-(4-methyl-1H-imidazol-5-yl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
10 d]pyrimidine-4,6(5H,7H)-dione,
2-(2,3-difluorobenzyl)-7-isobutyl-5-methyl-3-(4-pyridinyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
2-(2,4-dimethylbenzyl)-7-isobutyl-5-methyl-3-(4-pyridinyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
15 2-(3,5-dichlorobenzyl)-3-[3-(2-hydroxyethoxy)phenyl]-7-isobutyl-5-methyl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
2-(3,5-dichlorobenzyl)-7-isobutyl-3,5-dimethyl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
2-(3,5-dichlorobenzyl)-7-isobutyl-5-methyl-3-(1,3-thiazol-5-yl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
20 d]pyrimidine-4,6(5H,7H)-dione,
2-(3,5-dichlorobenzyl)-7-isobutyl-5-methyl-3-(1-methyl-1H-imidazol-2-yl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
2-(3,5-dichlorobenzyl)-7-isobutyl-5-methyl-3-(2-methyl-2H-isoindol-1-yl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
25 2-(3,5-dichlorobenzyl)-7-isobutyl-5-methyl-3-(4-methyl-1H-imidazol-5-yl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
2-(3,5-difluorobenzyl)-7-isobutyl-5-methyl-3-(4-pyridinyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
2-(3-{3-[benzyl(methyl)amino]-1-propynyl}benzyl)-7-isobutyl-5-methyl-3-(4-pyridinyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
30 pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
2-(3-aminobenzyl)-7-isobutyl-5-methyl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
2-(3-benzoylbenzyl)-3-[(3-hydroxypropyl)thio]-7-isobutyl-5-methyl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,

- 202 -

- 2-(3-bromobenzyl)-7-isobutyl-5-methyl-3-(4-pyridinyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
- 2-(3-fluoro-2-methylbenzyl)-7-isobutyl-5-methyl-3-(4-pyridinyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
- 5 2-(3-iodobenzyl)-7-isobutyl-5-methyl-3-(1-methyl-1H-imidazol-2-yl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
- 2-(3-iodobenzyl)-7-isobutyl-5-methyl-3-(4-pyridinyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
- 2-[(1-benzyl-1H-indol-3-yl)methyl]-3-(4-chloro-1-methyl-1H-pyrazol-3-yl)-7-isobutyl-5-methyl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
- 10 2-[(1-benzyl-1H-indol-3-yl)methyl]-3-[3-(2-hydroxyethoxy)phenyl]-7-isobutyl-5-methyl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
- 2-[(1-benzyl-1H-indol-3-yl)methyl]-7-isobutyl-5-methyl-3-(1-methyl-1H-pyrrol-2-yl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
- 15 2-[(4'-fluoro-1,1'-biphenyl-2-yl)methyl]-7-isobutyl-5-methyl-3-(1-methyl-1H-imidazol-2-yl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
- 2-[(4'-fluoro-1,1'-biphenyl-2-yl)methyl]-7-isobutyl-5-methyl-3-(1-methyl-1H-pyrrol-2-yl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
- 2-[(4'-fluoro-1,1'-biphenyl-2-yl)methyl]-7-isobutyl-5-methyl-3-(4-pyridinyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
- 20 2-[2-(allyloxy)benzyl]-3-cyclohexyl-7-isobutyl-5-methyl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
- 2-[2-(allyloxy)benzyl]-7-isobutyl-3,5-dimethyl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
- 25 2-[2-(allyloxy)benzyl]-7-isobutyl-5-methyl-3-(1,3-thiazol-2-yl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
- 2-[2-(allyloxy)benzyl]-7-isobutyl-5-methyl-3-(1-methyl-1H-imidazol-2-yl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
- 2-[2-(allyloxy)benzyl]-7-isobutyl-5-methyl-3-(1-methyl-1H-pyrrol-2-yl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
- 30 2-[2-(allyloxy)benzyl]-7-isobutyl-5-methyl-3-(4-methyl-1H-imidazol-5-yl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,

- 203 -

- 2-[2-(benzyloxy)benzyl]-3-(4-chloro-1-methyl-1H-pyrazol-3-yl)-7-isobutyl-5-methyl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
 2-[2-(benzyloxy)benzyl]-7-isobutyl-5-methyl-3-(1-methyl-1H-imidazol-2-yl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
 5 2-[2-(benzyloxy)benzyl]-7-isobutyl-5-methyl-3-(4-pyridinyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
 2-[2-fluoro-3-(trifluoromethyl)benzyl]-7-isobutyl-5-methyl-3-(4-pyridinyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
 2-[3-(3-hydroxy-1-butynyl)benzyl]-7-isobutyl-5-methyl-3-(4-pyridinyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
 10 d]pyrimidine-4,6(5H,7H)-dione,
 2-[3-(3-hydroxy-3-phenyl-1-propynyl)benzyl]-7-isobutyl-5-methyl-3-(4-pyridinyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
 2-[5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-3-(4-pyridinyl)-2,4,5,6-tetrahydro-7H-pyrazolo[3,4-d]pyrimidin-7-yl]butanenitrile,
 15 2-[5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-3-(4-pyridinyl)-2,4,5,6-tetrahydro-7H-pyrazolo[3,4-d]pyrimidin-7-yl]acetamide,
 2-[7-isobutyl-2-(1-naphthylmethyl)-4,6-dioxo-3-(4-pyridinyl)-2,4,6,7-tetrahydro-5H-pyrazolo[3,4-d]pyrimidin-5-yl]acetamide,
 2-[7-isobutyl-5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]benzoic acid,
 20 2-{3-[(3E)-5-hydroxy-3-penten-1-ynyl]benzyl}-7-isobutyl-5-methyl-3-(4-pyridinyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
 2-{3-[3-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-propynyl]benzyl}-7-isobutyl-5-methyl-3-(1-methyl-1H-imidazol-2-yl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
 25 2-{3-[3-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-propynyl]benzyl}-7-isobutyl-5-methyl-3-(4-pyridinyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
 2-{3-[3-(1H-1,2,3-benzotriazol-1-yl)-1-propynyl]benzyl}-7-isobutyl-5-methyl-3-(4-pyridinyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
 2-{3-[3-(dimethylamino)-1-propynyl]benzyl}-7-isobutyl-5-methyl-3-(4-pyridinyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
 30 2-benzyl-7-isobutyl-5-methyl-3-(4-pyridinyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,

- 204 -

- 3-(1,3-benzodioxol-4-yl)-2-(2,3-dichlorobenzyl)-7-isobutyl-5-methyl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
3-(1,3-benzodioxol-4-yl)-2-(3,5-dichlorobenzyl)-7-isobutyl-5-methyl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
5 3-(1,3-benzodioxol-4-yl)-7-isobutyl-5-methyl-2-(4-quinolinylmethyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
3-(1,5-dihydroxypentyl)-5-methyl-7-(2-methyl-2-propenyl)-2-(1-naphthylmethyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
3-(1-benzyl-1H-imidazol-2-yl)-7-isobutyl-5-methyl-2-(1-naphthylmethyl)-2H-pyrazolo[3,4-
10 d]pyrimidine-4,6(5H,7H)-dione,
3-(1H-imidazol-2-yl)-7-isobutyl-5-methyl-2-(1-naphthylmethyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
3-(2,2-difluoro-1,3-benzodioxol-5-yl)-7-isobutyl-5-methyl-2-(1-naphthylmethyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
15 3-(2-ethyl-4-methyl-1H-imidazol-5-yl)-7-isobutyl-5-methyl-2-(1-naphthylmethyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
3-(3-aminophenyl)-2-[(1-benzyl-1H-indol-3-yl)methyl]-7-isobutyl-5-methyl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
3-(3-aminophenyl)-7-isobutyl-2-[3-(4-methoxyphenoxy)benzyl]-5-methyl-2H-pyrazolo[3,4-
20 d]pyrimidine-4,6(5H,7H)-dione,
3-(3-aminophenyl)-7-isobutyl-5-methyl-2-[(2Z)-2-phenyl-2-pentenyl]-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
3-(3-aminophenyl)-7-isobutyl-5-methyl-2-[(2Z)-5-methyl-2-phenyl-2-hexenyl]-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
25 3-(3-aminophenyl)-7-isobutyl-5-methyl-2-[(4-phenyl-1H-pyrazol-3-yl)methyl]-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
3-(3-chlorophenyl)-7-isobutyl-5-methyl-2-(1-naphthylmethyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
3-(3-fluorophenyl)-7-isobutyl-5-methyl-2-(1-naphthylmethyl)-2H-pyrazolo[3,4-d]pyrimidine-
30 4,6(5H,7H)-dione,
3-(3-hydroxyphenyl)-7-isobutyl-5-methyl-2-(1-naphthylmethyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,

- 205 -

- 3-(4-butoxyphenyl)-7-isobutyl-5-methyl-2-(1-naphthylmethyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
- 3-(4-chloro-1-methyl-1H-pyrazol-3-yl)-2-[(4'-fluoro-1,1'-biphenyl-2-yl)methyl]-7-isobutyl-5-methyl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
- 5 3-(4-chloro-1-methyl-1H-pyrazol-3-yl)-7-isobutyl-2-[3-(4-methoxyphenoxy)benzyl]-5-methyl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
- 3-(4-chloro-1-methyl-1H-pyrazol-3-yl)-7-isobutyl-5-methyl-2-[(1-methyl-1H-indol-3-yl)methyl]-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
- 3-(4-chloro-1-methyl-1H-pyrazol-3-yl)-7-isobutyl-5-methyl-2-[(2Z)-2-phenyl-2-pentenyl]-
- 10 2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
- 3-(4-chloro-1-methyl-1H-pyrazol-3-yl)-7-isobutyl-5-methyl-2-[(2Z)-5-methyl-2-phenyl-2-hexenyl]-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
- 3-(4-chloro-1-methyl-4H-1lambda~5~-pyrazol-3-yl)-7-isobutyl-5-methyl-2-[(3-phenyl-1H-pyrazol-4-yl)methyl]-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
- 15 3-(4-fluorophenyl)-7-isobutyl-5-methyl-2-(1-naphthylmethyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
- 3-(4-hydroxybutyl)-7-isobutyl-5-methyl-2-(1-naphthylmethyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
- 3-(4-hydroxyphenyl)-7-isobutyl-5-methyl-2-(1-naphthylmethyl)-2H-pyrazolo[3,4-
- 20 d]pyrimidine-4,6(5H,7H)-dione,
- 3-(benzylthio)-7-isobutyl-5-methyl-2-(1-naphthylmethyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
- 3-[(3-hydroxypropyl)thio]-7-isobutyl-5-methyl-2-(1-naphthylmethyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
- 25 3-[(3-hydroxypropyl)thio]-7-isobutyl-5-methyl-2-(2-quinolinylmethyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
- 3-[(3-hydroxypropyl)thio]-7-isobutyl-5-methyl-2-{2-[(phenylsulfonyl)methyl]benzyl}-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
- 3-[2-(1-benzothien-3-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2H-
- 30 pyrazolo[3,4-d]pyrimidin-3-yl]benzoic acid,
- 3-[2-(2,3-dichlorobenzyl)-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]benzoic acid,

- 3-[3-(2-hydroxyethoxy)phenyl]-7-isobutyl-2-[(2-methoxy-1-naphthyl)methyl]-5-methyl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
3-[3-(2-hydroxyethoxy)phenyl]-7-isobutyl-2-[3-(4-methoxyphenoxy)benzyl]-5-methyl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
5 3-[3-(2-hydroxyethoxy)phenyl]-7-isobutyl-5-methyl-2-(1-naphthylmethyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
3-[3-(2-hydroxyethoxy)phenyl]-7-isobutyl-5-methyl-2-(4-quinolinylmethyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
3-[3-(2-hydroxyethoxy)phenyl]-7-isobutyl-5-methyl-2-[(2Z)-5-methyl-2-phenyl-2-hexenyl]-
10 2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
3-[3-(2-hydroxyethoxy)phenyl]-7-isobutyl-5-methyl-2-[(3-phenyl-1H-pyrazol-4-yl)methyl]-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
3-[4-(dimethylamino)phenyl]-7-isobutyl-5-methyl-2-(1-naphthylmethyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
15 3-[5,7-dimethyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]benzoic acid,
3-[5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]benzoic acid,
3-[5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-7-(2-phenoxyethyl)-4,5,6,7-tetrahydro-2H-
20 pyrazolo[3,4-d]pyrimidin-3-yl]benzoic acid,
3-[5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-7-(2-phenylpropyl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]benzoic acid,
3-[5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-7-(3-pyridinylmethyl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]benzoic acid,
25 3-[5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-7-(3-thienylmethyl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]benzoic acid,
3-[5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-7-(tetrahydro-2-furanylmethyl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]benzoic acid,
3-[5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-7-(tetrahydro-2H-pyran-2-ylmethyl)-4,5,6,7-
30 tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]benzoic acid,
3-[5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-7-pentyl-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]benzoic acid,

- 207 -

- 3-[5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-7-propyl-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]benzoic acid,
- 3-[5-methyl-7-(2-methylbenzyl)-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]benzoic acid,
- 5 3-[5-methyl-7-(3-methylbenzyl)-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]benzoic acid,
- 3-[5-methyl-7-[(6-methyl-2-pyridinyl)methyl]-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]benzoic acid,
- 3-[5-methyl-7-[2-(4-methyl-1,3-thiazol-5-yl)ethyl]-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]benzoic acid,
- 10 3-[7-(2,4-difluorobenzyl)-5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]benzoic acid,
- 3-[7-(2-bromobenzyl)-5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]benzoic acid,
- 3-[7-(2-chlorobenzyl)-5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]benzoic acid,
- 15 3-[7-(2-cyanoethyl)-5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]benzoic acid,
- 3-[7-(2-isopropoxyethyl)-5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]benzoic acid,
- 20 3-[7-(3,4-dimethylbenzyl)-5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]benzoic acid,
- 3-[7-(3-cyanobenzyl)-5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]benzoic acid,
- 25 3-[7-(3-cyclopentylpropyl)-5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]benzoic acid,
- 3-[7-(3-fluorobenzyl)-5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]benzoic acid,
- 3-[7-(4-butylbenzyl)-5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]benzoic acid,
- 30 3-[7-(4-chlorobenzyl)-5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]benzoic acid,

- 208 -

- 3-[7-(4-ethylbenzyl)-5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]benzoic acid,
- 3-[7-(cyclobutylmethyl)-5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]benzoic acid,
- 5 3-[7-(cyclohexylmethyl)-5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]benzoic acid,
- 3-[7-(cyclopropylmethyl)-5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]benzoic acid,
- 3-[7-[(3,5-dimethyl-4-isoxazolyl)methyl]-5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]benzoic acid,
- 10 3-[7-[(5-chloro-2-thienyl)methyl]-5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]benzoic acid,
- 3-[7-[2-(3-chlorophenyl)ethyl]-5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]benzoic acid,
- 15 3-[7-[2-(diethylamino)-2-oxoethyl]-5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]benzoic acid,
- 3-[7-[2-(isobutylthio)ethyl]-5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]benzoic acid,
- 3-[7-[2-(isonicotinoylamino)ethyl]-5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]benzoic acid,
- 20 3-[7-{2-[benzyl(methyl)amino]ethyl}-5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]benzoic acid,
- 3-[7-benzyl-5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]benzoic acid,
- 25 3-[7-isobutyl-5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]benzonitrile,
- 3-[7-isobutyl-5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]benzamide,
- 3-[7-isobutyl-5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]-N-methylbenzamide,
- 30 3-[7-isobutyl-5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]benzoic acid,

- 209 -

- 3-[7-isobutyl-5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]phenylboronic acid,
3-[7-isobutyl-5-methyl-4,6-dioxo-2-(4-quinolinylmethyl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]benzoic acid,
5 3-[7-isopentyl-5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]benzoic acid,
3-[7-isopropyl-5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]benzoic acid,
3-[hydroxy(phenyl)methyl]-7-isobutyl-5-methyl-2-(1-naphthylmethyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
10 3-{[7-isobutyl-5-methyl-4,6-dioxo-3-(4-pyridinyl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-2-yl]methyl}benzonitrile,
3-{2-[(4'-fluoro-1,1'-biphenyl-2-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl}benzoic acid,
15 3-{2-[(4-fluoro-1-naphthyl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl}benzoic acid,
3-{2-[2-(benzyloxy)benzyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl}benzoic acid,
3-{5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-7-[2-(2-thienyl)ethyl]-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl}benzoic acid,
20 3-{7-isobutyl-2-[(2-methoxy-1-naphthyl)methyl]-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl}benzoic acid,
3-{7-isobutyl-2-[3-(4-methoxyphenoxy)benzyl]-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl}benzoic acid,
25 3-{7-isobutyl-5-methyl-2-[(2Z)-5-methyl-2-phenyl-2-hexenyl]-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl}benzoic acid,
3-{7-isobutyl-5-methyl-4,6-dioxo-2-[(3-phenyl-1H-pyrazol-4-yl)methyl]-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl}benzoic acid,
3-cyclohexyl-2-(3,5-dichlorobenzyl)-7-isobutyl-5-methyl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
30 3-cyclohexyl-7-isobutyl-2-[(2-methoxy-1-naphthyl)methyl]-5-methyl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,

- 3-cyclohexyl-7-isobutyl-5-methyl-2-(4-quinolinylmethyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
- 4-[7-isobutyl-5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]benzoic acid,
- 5 4-{[5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-3-(4-pyridinyl)-2,4,5,6-tetrahydro-7H-pyrazolo[3,4-d]pyrimidin-7-yl]methyl}phenyl acetate,
- 4-{[7-isobutyl-5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]thio}butanoic acid,
- 4-bromo-3-[(7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-2-yl)methyl]benzoic acid,
- 10 5-(2-hydroxyethyl)-7-isobutyl-2-(1-naphthylmethyl)-3-(4-pyridinyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
- 5,7-dimethyl-2-(1-naphthylmethyl)-3-(4-pyridinyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
- 15 5-[2-(dimethylamino)ethyl]-7-isobutyl-2-(1-naphthylmethyl)-3-(4-pyridinyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
- 5-[7-isobutyl-5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]-3-thiophenecarboxylic acid,
- 5-[7-isobutyl-5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-thiophenecarboxylic acid,
- 20 5-{2-[2-(benzyloxy)benzyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl}-2-furoic acid,
- 5-{7-isobutyl-2-[3-(4-methoxyphenoxy)benzyl]-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl}-2-furoic acid,
- 25 5-{7-isobutyl-5-methyl-2-[(2Z)-5-methyl-2-phenyl-2-hexenyl]-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl}-2-furoic acid,
- 5-{7-isobutyl-5-methyl-4,6-dioxo-2-[(2Z)-2-phenyl-2-pentenyl]-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl}-2-furoic acid,
- 5-methyl-2-(1-naphthylmethyl)-3-(4-pyridinyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
- 30 5-methyl-2-(1-naphthylmethyl)-3-(4-pyridinyl)-7-(2-pyridinylmethyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,

- 211 -

- 5-methyl-2-(1-naphthylmethyl)-3-(4-pyridinyl)-7-(4-pyridinylmethyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
5-methyl-2-(1-naphthylmethyl)-3-(4-pyridinyl)-7-(tetrahydro-2H-pyran-2-ylmethyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
5 5-methyl-2-(1-naphthylmethyl)-3-(4-pyridinyl)-7-[2-(trifluoromethyl)benzyl]-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
5-methyl-2-(1-naphthylmethyl)-3-(4-pyridinyl)-7-[3-(1H-pyrrol-1-yl)propyl]-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
5-methyl-2-(1-naphthylmethyl)-3-(4-pyridinyl)-7-[4-(trifluoromethoxy)benzyl]-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
10 5-methyl-2-(1-naphthylmethyl)-3-(4-pyridinyl)-7-[[trifluoromethylthio]methyl]-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
5-methyl-2-(1-naphthylmethyl)-3-(4-pyridinyl)-7-[[trifluoromethylsulfonyl]methyl]-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
15 5-methyl-2-(1-naphthylmethyl)-3-(4-pyridinyl)-7-[[trifluoromethylsulfinyl]methyl]-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
5-methyl-2-(1-naphthylmethyl)-7-(2-oxopropyl)-3-(4-pyridinyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
5-methyl-2-(1-naphthylmethyl)-7-(2-phenylethyl)-3-(4-pyridinyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
20 5-methyl-2-(1-naphthylmethyl)-7-[(phenylsulfinyl)methyl]-3-(4-pyridinyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
5-methyl-2-(1-naphthylmethyl)-7-[(phenylthio)methyl]-3-(4-pyridinyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
25 5-methyl-2-(1-naphthylmethyl)-7-[2-(1-piperidinyl)ethyl]-3-(4-pyridinyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
5-methyl-2-(1-naphthylmethyl)-7-pentyl-3-(4-pyridinyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
5-methyl-7-(2-methyl-2-propenyl)-2-(1-naphthylmethyl)-3-(2-pyridinyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
30 5-methyl-7-(2-methylbenzyl)-2-(1-naphthylmethyl)-3-(4-pyridinyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,

- 212 -

- 5-methyl-7-(3-methyl-2-butenyl)-2-(1-naphthylmethyl)-3-(4-pyridinyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
5-methyl-7-(3-methylbenzyl)-2-(1-naphthylmethyl)-3-(4-pyridinyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
5 5-methyl-7-(5-methyl-2-nitrobenzyl)-2-(1-naphthylmethyl)-3-(4-pyridinyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
5-methyl-7-[(1-methyl-3-piperidinyl)methyl]-2-(1-naphthylmethyl)-3-(4-pyridinyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
5-methyl-7-[(6-methyl-2-pyridinyl)methyl]-2-(1-naphthylmethyl)-3-(4-pyridinyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
10 5-methyl-7-[(methylsulfinyl)methyl]-2-(1-naphthylmethyl)-3-(4-pyridinyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
5-methyl-7-[(methylsulfonyl)methyl]-2-(1-naphthylmethyl)-3-(4-pyridinyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione 1-oxide,
15 5-methyl-7-[(methylthio)methyl]-2-(1-naphthylmethyl)-3-(4-pyridinyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
5-methyl-7-[2-(4-methyl-1,3-thiazol-5-yl)ethyl]-2-(1-naphthylmethyl)-3-(4-pyridinyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
5-methyl-7-[2-(4-morpholinyl)ethyl]-2-(1-naphthylmethyl)-3-(4-pyridinyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
20 5-methyl-7-{2-[1-(methylsulfonyl)-4-piperidinyl]ethyl}-2-(1-naphthylmethyl)-3-(4-pyridinyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
5-methyl-7-{2-methyl-3-[2-(4-morpholinyl)-2-oxoethoxy]benzyl}-2-(1-naphthylmethyl)-3-(4-pyridinyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
25 5-methyl-7-{2-methyl-3-[2-(4-morpholinyl)ethoxy]benzyl}-2-(1-naphthylmethyl)-3-(4-pyridinyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
7-(2,3-dihydro-1,4-benzodioxin-5-ylmethyl)-5-methyl-2-(1-naphthylmethyl)-3-(4-pyridinyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
7-(2,6-dichlorobenzyl)-5-methyl-2-(1-naphthylmethyl)-3-(4-pyridinyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
30 7-(2,6-dimethylbenzyl)-5-methyl-2-(1-naphthylmethyl)-3-(4-pyridinyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,

- 213 -

- 7-(2-butynyl)-5-methyl-2-(1-naphthylmethyl)-3-(4-pyridinyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
- 7-(2-chlorobenzyl)-5-methyl-2-(1-naphthylmethyl)-3-(4-pyridinyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
- 5 7-(2-hydroxyethyl)-5-methyl-2-(1-naphthylmethyl)-3-(4-pyridinyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
- 7-(3-isobutoxy-2-methylbenzyl)-5-methyl-2-(1-naphthylmethyl)-3-(4-pyridinyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
- 7-(3-isobutoxybenzyl)-5-methyl-2-(1-naphthylmethyl)-3-(4-pyridinyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
- 10 d]pyrimidine-4,6(5H,7H)-dione,
- 7-(4-isopropylbenzyl)-5-methyl-2-(1-naphthylmethyl)-3-(4-pyridinyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
- 7-[(3,5-dimethyl-4-isoxazolyl)methyl]-5-methyl-2-(1-naphthylmethyl)-3-(4-pyridinyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
- 15 7-[(4-chloro-3-methyl-2-pyridinyl)methyl]-5-methyl-2-(1-naphthylmethyl)-3-(4-pyridinyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
- 7-[(6-fluoro-4H-1,3-benzodioxin-8-yl)methyl]-5-methyl-2-(1-naphthylmethyl)-3-(4-pyridinyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
- 7-[2-(dimethylamino)ethyl]-5-methyl-2-(1-naphthylmethyl)-3-(4-pyridinyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
- 20 d]pyrimidine-4,6(5H,7H)-dione,
- 7-allyl-5-methyl-2-(1-naphthylmethyl)-3-(4-pyridinyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
- 7-benzyl-5-methyl-2-(1-naphthylmethyl)-3-(4-pyridinyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
- 25 7-isobutyl-2-(1-naphthylmethyl)-3-(4-pyridinyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
- 7-isobutyl-2-(1-naphthylmethyl)-3-(4-pyridinyl)-5-(2-pyridinylmethyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
- 7-isobutyl-2-(1-naphthylmethyl)-3-(4-pyridinyl)-5-(4-pyridinylmethyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
- 30 d]pyrimidine-4,6(5H,7H)-dione,
- 7-isobutyl-2-(1-naphthylmethyl)-5-[2-(1-piperidinyl)ethyl]-3-(4-pyridinyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,

- 214 -

- 7-isobutyl-2-(3-{3-[(mesitylmethyl)amino]-1-propynyl}benzyl)-5-methyl-3-(1-methyl-1H-imidazol-2-yl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
7-isobutyl-2-(3-{3-[(mesitylmethyl)amino]-1-propynyl}benzyl)-5-methyl-3-(4-pyridinyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
5 7-isobutyl-2-[(2-methoxy-1-naphthyl)methyl]-5-methyl-3-(1-methyl-1H-imidazol-2-yl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
7-isobutyl-2-[(2-methoxy-1-naphthyl)methyl]-5-methyl-3-(5-methyl-1H-imidazol-4-yl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
7-isobutyl-2-[3-(3-methoxy-1-propynyl)benzyl]-5-methyl-3-(1-methyl-1H-imidazol-2-yl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
10 7-isobutyl-2-[3-(3-methoxy-1-propynyl)benzyl]-5-methyl-3-(4-pyridinyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
7-isobutyl-2-[3-(4-methoxyphenoxy)benzyl]-5-methyl-3-(1-methyl-1H-imidazol-2-yl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
15 7-isobutyl-3-(3-methoxyphenyl)-5-methyl-2-(1-naphthylmethyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
7-isobutyl-3,5-dimethyl-2-(1-naphthylmethyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
7-isobutyl-3,5-dimethyl-2-(4-quinolinylmethyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
20 7-isobutyl-5-[2-(4-morpholinyl)ethyl]-2-(1-naphthylmethyl)-3-(4-pyridinyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
7-isobutyl-5-methyl-2-(1-naphthylmethyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
7-isobutyl-5-methyl-2-(1-naphthylmethyl)-3-(1,3-thiazol-2-yl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
25 7-isobutyl-5-methyl-2-(1-naphthylmethyl)-3-(2-phenyl-1H-imidazol-4-yl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
7-isobutyl-5-methyl-2-(1-naphthylmethyl)-3-(2-phenylethyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
30 7-isobutyl-5-methyl-2-(1-naphthylmethyl)-3-(2-thienyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
7-isobutyl-5-methyl-2-(1-naphthylmethyl)-3-(3-nitrophenyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,

- 215 -

- 7-isobutyl-5-methyl-2-(1-naphthylmethyl)-3-(3-phenoxyphenyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
7-isobutyl-5-methyl-2-(1-naphthylmethyl)-3-(3-pyridinyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
5 7-isobutyl-5-methyl-2-(1-naphthylmethyl)-3-(3-thienyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
7-isobutyl-5-methyl-2-(1-naphthylmethyl)-3-(4-nitrophenyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
7-isobutyl-5-methyl-2-(1-naphthylmethyl)-3-(4-pyridinyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
10 4,6(5H,7H)-dione,
7-isobutyl-5-methyl-2-(1-naphthylmethyl)-3-(propylthio)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
7-isobutyl-5-methyl-2-(1-naphthylmethyl)-3-[3-(1H-tetrazol-5-yl)phenyl]-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
15 7-isobutyl-5-methyl-2-(1-naphthylmethyl)-3-[3-(trifluoromethyl)phenyl]-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
7-isobutyl-5-methyl-2-(1-naphthylmethyl)-3-[4-(trifluoromethyl)phenyl]-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
7-isobutyl-5-methyl-2-(1-naphthylmethyl)-3-phenyl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
20 4,6(5H,7H)-dione,
7-isobutyl-5-methyl-2-(1-naphthylsulfonyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
7-isobutyl-5-methyl-2-(2-naphthylmethyl)-3-(4-pyridinyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
7-isobutyl-5-methyl-2-(3-phenoxybenzyl)-3-(4-pyridinyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
25 4,6(5H,7H)-dione,
7-isobutyl-5-methyl-2-(4-quinolinylmethyl)-3-(1,3-thiazol-5-yl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
7-isobutyl-5-methyl-2-[(2Z)-5-methyl-2-phenyl-2-hexenyl]-3-(4-pyridinyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
30 7-isobutyl-5-methyl-2-[1-(1-naphthyl)-2-phenylethyl]-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
7-isobutyl-5-methyl-2-[3-(3-phenyl-1-propynyl)benzyl]-3-(4-pyridinyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,

- 216 -

- 7-isobutyl-5-methyl-2-{3-[3-(methylamino)-1-propynyl]benzyl}-3-(4-pyridinyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
7-isobutyl-5-methyl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
7-isobutyl-5-methyl-3-(1-methyl-1H-benzimidazol-2-yl)-2-(1-naphthylmethyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
5 7-isobutyl-5-methyl-3-(1-methyl-1H-imidazol-2-yl)-2-(1-naphthylmethyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
7-isobutyl-5-methyl-3-(1-methyl-1H-imidazol-2-yl)-2-(4-quinolinylmethyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
10 7-isobutyl-5-methyl-3-(1-methyl-1H-imidazol-2-yl)-2-[(2Z)-2-phenyl-2-pentenyl]-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
7-isobutyl-5-methyl-3-(1-methyl-1H-imidazol-2-yl)-2-[(2Z)-5-methyl-2-phenyl-2-hexenyl]-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
7-isobutyl-5-methyl-3-(1-methyl-1H-imidazol-2-yl)-2-[(3-phenyl-1H-pyrazol-4-yl)methyl]-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
15 7-isobutyl-5-methyl-3-(1-methyl-1H-indol-2-yl)-2-(1-naphthylmethyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
7-isobutyl-5-methyl-3-(1-methyl-1H-indol-3-yl)-2-(1-naphthylmethyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
20 7-isobutyl-5-methyl-3-(1-methyl-1H-pyrrol-2-yl)-2-(4-quinolinylmethyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
7-isobutyl-5-methyl-3-(1-methyl-1H-pyrrol-2-yl)-2-[(3-phenyl-1H-pyrazol-4-yl)methyl]-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
7-isobutyl-5-methyl-3-(2-methyl-2H-isoindol-1-yl)-2-(4-quinolinylmethyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
25 7-isobutyl-5-methyl-3-(3-methyl-2-thienyl)-2-(1-naphthylmethyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
7-isobutyl-5-methyl-3-(4-methyl-1H-imidazol-5-yl)-2-(4-quinolinylmethyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
30 7-isobutyl-5-methyl-3-(4-pyridinyl)-2-(4-quinolinylmethyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
7-isobutyl-5-methyl-3-(4-pyridinyl)-2-[2-(trifluoromethoxy)benzyl]-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,

- 217 -

- 7-isobutyl-5-methyl-3-(4-pyridinyl)-2-[3-(trifluoromethoxy)benzyl]-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
 7-isobutyl-5-methyl-3-(4-pyridinyl)-2-[3-(trifluoromethyl)benzyl]-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
 5 7-isobutyl-5-methyl-3-(6-methyl-2-pyridinyl)-2-(1-naphthylmethyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
 7-isobutyl-5-methyl-3-(methylthio)-2-(1-naphthylmethyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
 7-isobutyl-5-methyl-3-[4-(methylsulfonyl)phenyl]-2-(1-naphthylmethyl)-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione,
 10 methyl [(2-methyl-3-{[5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-3-(4-pyridinyl)-2,4,5,6-tetrahydro-7H-pyrazolo[3,4-d]pyrimidin-7-yl]methyl}phenyl)thio]acetate,
 methyl 3-[2-(3-{3-[benzyl(methyl)amino]-1-propynyl}benzyl)-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]benzoate,
 15 methyl 3-[2-(3-bromobenzyl)-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]benzoate,
 methyl 3-[2-(3-iodobenzyl)-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]benzoate,
 methyl 3-[7-isobutyl-2-(1-naphthylmethyl)-4,6-dioxo-3-(4-pyridinyl)-2,4,6,7-tetrahydro-5H-pyrazolo[3,4-d]pyrimidin-5-yl]propanoate,
 20 methyl 3-[7-isobutyl-5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]benzoate,
 methyl 3-{[5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-3-(4-pyridinyl)-2,4,5,6-tetrahydro-7H-pyrazolo[3,4-d]pyrimidin-7-yl]methyl}benzoate,
 25 methyl 3-{2-[3-(3-hydroxy-1-butynyl)benzyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl}benzoate,
 methyl 3-{7-isobutyl-2-[3-(3-methoxy-1-propynyl)benzyl]-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl}benzoate,
 methyl 4-{[7-isobutyl-5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]thio}butanoate,
 30 N-(4-{2-[(1-benzyl-1H-indol-3-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)acetamide,

- 218 -

- N-(4-{2-[(4'-fluoro-1,1'-biphenyl-2-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)acetamide,
- N-(4-{2-[2-(allyloxy)benzyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)acetamide,
- 5 N-(4-{7-isobutyl-2-[(2-methoxy-1-naphthyl)methyl]-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)acetamide,
- N-(4-{7-isobutyl-2-[3-(4-methoxyphenoxy)benzyl]-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)acetamide,
- N-(4-{7-isobutyl-5-methyl-2-[(1-methyl-1H-indol-3-yl)methyl]-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)acetamide,
- 10 N-(4-{7-isobutyl-5-methyl-2-[(2Z)-5-methyl-2-phenyl-2-hexenyl]-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)acetamide,
- N-(4-{7-isobutyl-5-methyl-4,6-dioxo-2-[(2Z)-2-phenyl-2-pentenyl]-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)acetamide,
- 15 N-(4-{7-isobutyl-5-methyl-4,6-dioxo-2-[(3-phenyl-1H-pyrazol-4-yl)methyl]-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)acetamide,
- N,N-diethyl-2-[7-isobutyl-2-(1-naphthylmethyl)-4,6-dioxo-3-(4-pyridinyl)-2,4,6,7-tetrahydro-5H-pyrazolo[3,4-d]pyrimidin-5-yl]acetamide,
- N-[2-({[5-(dimethylamino)-1-naphthyl]sulfonyl}amino)ethyl]-3-[7-isobutyl-5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]benzamide,
- 20 N-[3-(3-{[7-isobutyl-5-methyl-3-(1-methyl-1H-imidazol-2-yl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-2-yl]methyl}phenyl)-2-propynyl]-5-methyl-3-phenyl-4-isoxazolecarboxamide,
- N-[4-[2-(1-benzothien-3-yl)methyl]-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]phenyl}acetamide,
- 25 N-{4-[2-(2,3-dichlorobenzyl)-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]phenyl}acetamide,
- N-{4-[2-(3,5-dichlorobenzyl)-7-isobutyl-5-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]phenyl}acetamide,
- 30 N-{4-[7-isobutyl-5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]phenyl}acetamide,
- N-{4-[7-isobutyl-5-methyl-4,6-dioxo-2-(4-quinolinylmethyl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-d]pyrimidin-3-yl]phenyl}acetamide,

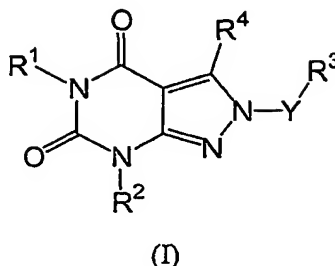
- 219 -

tert-butyl [5-methyl-2-(1-naphthylmethyl)-4,6-dioxo-3-(4-pyridinyl)-2,4,5,6-tetrahydro-7H-pyrazolo[3,4-d]pyrimidin-7-yl]acetate,

- 220 -

CLAIMS:

1. A compound of formula (I)



5

wherein,

R^1 is H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted cycloalkynyl, optionally substituted aryl, optionally substituted alkoxy, amino, or optionally substituted heterocycle;

R^2 is H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted cycloalkynyl, optionally substituted aryl, optional substituted alkoxy, amino, or optionally substituted heterocycle;

R^3 is a monocyclic or bicyclic, saturated or unsaturated, ring system comprising 0, 1, 2 or 3 of heteroatoms independently selected from N, O, or S, the ring being substituted by 0, 1, 2 or 3 substituents selected from =O, halogen, $-OR^a$, C_{1-6} alkyl, C_{1-6} haloalkyl, -CN, nitro, , $-S(=O)_nR^c$, $-O(CH_2)_mHet$, $-O(CH_2)_mC(=O)Het$, $-O(CH_2)_mC(=O)NR^aR^a$, $-O(CH_2)_mC(=O)OR^a$, $-O(CH_2)_mNR^aR^a$, $-O(CH_2)_mOR^a$, $-S(CH_2)_mHet$, $-S(CH_2)_mC(=O)Het$, $-S(CH_2)_mC(=O)NR^aR^a$, $-S(CH_2)_mC(=O)OR^a$, $-S(CH_2)_mNR^aR^a$, $-S(CH_2)_mOR^a$, $-NHR^a$, $-NR^a_2$, $-NHC(=O)R^a$, $N=NR^a$, aminocarbonyl, phenyl or benzyl;

R^4 is C_{1-6} alkyl, $-NC_{1-6}$ alkyl, or $-N(C_{1-6}alkyl)_2$ wherein the C_{1-6} alkyl, $-NC_{1-6}alkyl$, $-N(C_{1-6}alkyl)_2$ are substituted by 0, 1 or 2 substituents selected from R^a , OR^a , halogen or phenyl wherein R^4 is not $-(CH_2)_zCH_3$, $-(CH_2)_zCH_2OH$, $-(CH_2)_zCO_2H$, or $-(CH_2)_zCO_2C_{1-6}alkyl$ wherein z is 1, 2, 3, 4, 5, or 6;

R^5 is independently at each instance, phenyl substituted by 0, 1, 2, or 3 groups selected from halogen, C_{1-6} haloalkyl, $-OC_{1-6}haloalkyl$, C_{1-6} alkyl, -CN, nitro, -OH, $-OR^c$, $-S(=O)_nR^c$, $-O(CH_2)_mHet$, $-O(CH_2)_mC(=O)Het$, $-O(CH_2)_mC(=O)NR^aR^a$, $-O(CH_2)_mC(=O)OR^a$, $-O(CH_2)_mNR^aR^a$, $-O(CH_2)_mOR^a$, $-S(CH_2)_mHet$, $-S(CH_2)_mC(=O)Het$, $-S(CH_2)_mC(=O)NR^aR^a$,

- 221 -

-S(CH₂)_mC(=O)OR^a, -S(CH₂)_mNR^aR^a, -S(CH₂)_mOR^a, -R^bOR^a, -SR^a, -C(=O)NR^aR^a, -C(=O)NR^aOR^a, -C(=O)NR^aR^bNR^aR^a, -C(=O)NR^aR^bOR^a, -C(=O)NR^aR^bS(=O)_nR^a, -C(=O)NR^aR^bHet, -C(=O)OR^a, -OC(=O)R^a, -C(=O)OR^bNR^aR^a, -C(=O)R^a, -C(=O)R^bNR^aR^a, -C(=NOR^a)R^a, -C(=NCN)R^a, -S(=O)₂NR^aR^a, -NR^aS(=O)₂R^a, -S(=O)₂NR^aR^bC(=O)NR^aR^a, or -S(=O)₂NR^aR^bC(=O)OR^a;

R^a is, independently at each instance, H, C₁₋₆alkyl, -C(=O)C₁₋₄alkyl, C₁₋₄haloalkyl, -(CH₂)_q-, phenyl, benzyl, or 5 or 6-membered ring, saturated or unsaturated heterocycle containing 1, 2, 3, or 4 heteroatoms independently selected from N, O or S and wherein q is 0, 1, 2, 3, 4, 5 or 6;

10 R^b is, independently at each instance C₁₋₆alkyl, -C(=O)C₁₋₄alkyl, C₁₋₄haloalkyl, -(CH₂)_q-, phenyl, benzyl, or 5 or 6-membered ring, saturated or unsaturated heterocycle containing 1, 2, 3, or 4 heteroatoms independently selected from N, O or S and wherein q is 0, 1, 2, 3, 4, 5 or 6;

R^c is C₁₋₆alkyl, C₁₋₄haloalkyl, phenyl or benzyl;

15 R^d is phenyl substituted by 0, 1, 2 or 3 groups selected from -CN, halogen, nitro, C₁₋₆alkyl, C₁₋₄haloalkyl, -OH, -OR^c, -NR^aR^b, -S(=O)_nR^c, -C(=O)R^a, -S(=O)NR^aR^b, -C(=O)NR^aR^a, -C(=O)OR^a, -NR^aC(=O)R^a, -OC(=O)R^a, B(OH)₂, vicinal -OCH₂CH₂O-, vicinal -OC₁₋₂haloalkylO-, vicinal -OCH₂O-, vicinal -CH₂OCH₂O-, phenyl, benzyl and a 5- or 6-membered ring, saturated or unsaturated heterocycle containing 1, 2, 3 or 4 heteroatoms

20 independently selected from N, O, or S;

Y is CH₂, CHCH₃, S(=O) or S(=O)₂;

m is 1, 2 or 3;

n is 0, 1 or 2; and

Het, unless otherwise defined, is a 5- or 6-membered ring, saturated or unsaturated

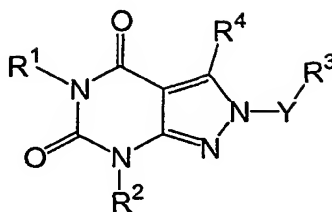
25 heterocycle containing 1, 2, 3 or 4 heteroatoms independently selected from N, O, or S, and substituted by 0, 1, 2 or 3 substituents selected from halogen, -(CH₂)_nR^d, C₁₋₄alkyl, -S(=O)_nR^c, -C(=O)R^a, or -S(=O)₂NR^aR^a vicinal -OCH₂CH₂O-, vicinal -OC₁₋₂haloalkylO-, vicinal -OCH₂O-, or vicinal -CH₂OCH₂O-, =O, halogen, cyano, -R^bOR^a, -R^bSR^a, -SR^a, -OR^a, C₁₋₆alkyl, C₁₋₆haloalkyl, -CN, nitro, -OH, -NHR^a, -NR^a₂, -NHC(=O)R^a, N=NR^a, -C(=O)NR^aR^a, -C(=O)NR^aOR^a, -C(=O)NR^aR^bNR^aR^a, -C(=O)NR^aR^bOR^a, -C(=O)NR^aR^bS(=O)_nR^a, -C(=O)NR^aR^bHet, -C(=O)OR^a, -OC(=O)R^a, -C(=O)OR^bNR^aR^a, -C(=O)R^bNR^aR^a, -C(=NOR^a)R^a, -C(=NCN)R^a, -NR^aS(=O)₂R^a, -S(=O)₂NR^aR^bC(=O)NR^aR^a, or -S(=O)₂NR^aR^bC(=O)OR^a;

30

- 222 -

or a pharmaceutically acceptable salt thereof.

2. A compound of formula (I)



(I)

wherein,

R¹ is H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted cycloalkynyl, optionally substituted aryl, optionally substituted alkoxy, amino, or optionally substituted heterocycle;

R² is H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted cycloalkynyl, optionally substituted aryl, optionally substituted alkoxy, amino, or optionally substituted heterocycle;

R³ is a monocyclic or bicyclic, saturated or unsaturated, ring system comprising 0, 1, 2 or 3 of heteroatoms independently selected from N, O, or S, the ring being substituted by 0, 1, 2 or 3 substituents selected from =O, halogen, -OR^a, C₁₋₆alkyl, C₁₋₆haloalkyl, -CN, nitro, , -S(=O)_nR^c, -O(CH₂)_mHet, -O(CH₂)_mC(=O)Het, -O(CH₂)_mC(=O)NR^aR^a, -O(CH₂)_mC(=O)OR^a, -O(CH₂)_mNR^aR^a, -O(CH₂)_mOR^a, -S(CH₂)_mHet, -S(CH₂)_mC(=O)Het, -S(CH₂)_mC(=O)NR^aR^a, -S(CH₂)_mC(=O)OR^a, -S(CH₂)_mNR^aR^a, -S(CH₂)_mOR^a, -NHR^a, -NR^a₂, -NHC(=O)R^a, N=NR^a, aminocarbonyl, phenyl or benzyl; or R³ is represented by -Het, -Het-Het, R⁵, R⁵-Het, -Het-R⁵, -Het-O-R⁵, -phenyl-R⁵ or -phenyl-OR⁵;

R⁴ is -(CH₂)_nphenyl-Het, -(CH₂)_nR^d, -Het, -Het-Het, R⁵, -R⁵-Het, -Het-R⁵, -Het-O-R⁵, -phenyl-R⁵ or -phenyl-OR⁵ or a monocyclic or bicyclic, saturated or unsaturated, ring system, or a vicinal-fused derivative thereof, which may contain from 5 to 12, preferably 5 to 10, ring atoms, 0, 1, 2, 3 or 4 of which are heteroatoms independently selected from N, O, or S, the ring system being substituted by 0, 1, 2 or 3 substituents selected from B(OH)₂, vicinal -OCH₂CH₂O-, vicinal -OC₁₋₂haloalkylO-, vicinal -OCH₂O-, vicinal -CH₂OCH₂O-, =O,

- 223 -

- halogen, $-R^bOR^a$, $-SR^a$, $-OR^a$, $C_{1-6}alkyl$, $C_{1-6}haloalkyl$, $-CN$, $-S(=O)_nR^c$, $-O(CH_2)_mHet$, $-O(CH_2)_mC(=O)Het$, $-O(CH_2)_mC(=O)NR^aR^a$, $-O(CH_2)_mC(=O)OR^a$, $-O(CH_2)_mNR^aR^a$, $-O(CH_2)_mOR^a$, $-S(CH_2)_mHet$, $-S(CH_2)_mC(=O)Het$, $-S(CH_2)_mC(=O)NR^aR^a$, $-S(CH_2)_mC(=O)OR^a$, $-S(CH_2)_mNR^aR^a$, $-S(CH_2)_mOR^a$, $-NHR^a$, $-NR^a_2$, $-NHC(=O)R^a$, $N=NR^a$, NO_2 , $-C(=O)NR^aR^a$, $-C(=O)NR^aOR^a$, $-C(=O)NR^aR^bNR^aR^a$, $-C(=O)NR^aR^bOR^a$, $-C(=O)NR^aR^bS(=O)_nR^a$, $-C(=O)NR^aR^bHet$, $-C(=O)OR^a$, $-OC(=O)R^a$, $-C(=O)OR^bNR^aR^a$, $-C(=O)R^a$, $-C(=O)R^bNR^aR^a$, $-C(=NOR^a)R^a$, $-C(=NCN)R^a$, $-S(=O)_2NR^aR^a$, $-NR^aS(=O)_2R^a$, $-S(=O)_2NR^aR^bC(=O)NR^aR^a$, $-S(=O)_2NR^aR^bC(=O)OR^a$, aminocarbonyl, phenyl or benzyl;
- R^5 is independently at each instance, phenyl substituted by 0, 1, 2, or 3 groups selected from halogen, $C_{1-6}haloalkyl$, $-OC_{1-6}haloalkyl$, $C_{1-6}alkyl$, $-CN$, nitro, $-OH$, $-OR^c$, $-S(=O)_nR^c$, $-O(CH_2)_mHet$, $-O(CH_2)_mC(=O)Het$, $-O(CH_2)_mC(=O)NR^aR^a$, $-O(CH_2)_mC(=O)OR^a$, $-O(CH_2)_mNR^aR^a$, $-O(CH_2)_mOR^a$, $-S(CH_2)_mHet$, $-S(CH_2)_mC(=O)Het$, $-S(CH_2)_mC(=O)NR^aR^a$, $-S(CH_2)_mC(=O)OR^a$, $-S(CH_2)_mNR^aR^a$, $-S(CH_2)_mOR^a$, $-R^bOR^a$, $-SR^a$, $-C(=O)NR^aR^a$, $-C(=O)NR^aOR^a$, $-C(=O)NR^aR^bNR^aR^a$, $-C(=O)NR^aR^bOR^a$, $-C(=O)NR^aR^bS(=O)_nR^a$, $-C(=O)NR^aR^bHet$, $-C(=O)OR^a$, $-OC(=O)R^a$, $-C(=O)OR^bNR^aR^a$, $-C(=O)R^a$, $-C(=O)R^bNR^aR^a$, $-C(=NOR^a)R^a$, $-C(=NCN)R^a$, $-S(=O)_2NR^aR^a$, $-NR^aS(=O)_2R^a$, $-S(=O)_2NR^aR^bC(=O)NR^aR^a$, $-S(=O)_2NR^aR^bC(=O)OR^a$;
- R^a is, independently at each instance, H, $C_{1-6}alkyl$, $-C(=O)C_{1-4}alkyl$, $C_{1-4}haloalkyl$, $(CH_2)_q$ -, phenyl, benzyl, or 5 or 6-membered ring, saturated or unsaturated heterocycle containing 1, 2, 3, or 4 heteroatoms independently selected from N, O or S and wherein q is 0, 1, 2, 3, 4, 5 or 6;
- R^b is, independently at each instance $C_{1-6}alkyl$, $-C(=O)C_{1-4}alkyl$, $C_{1-4}haloalkyl$, $(CH_2)_q$ -, phenyl, benzyl, or 5 or 6-membered ring, saturated or unsaturated heterocycle containing 1, 2, 3, or 4 heteroatoms independently selected from N, O or S and wherein q is 0, 1, 2, 3, 4, 5 or 6;
- R^c is $C_{1-6}alkyl$, $C_{1-4}haloalkyl$, phenyl or benzyl;
- R^d is phenyl substituted by 0, 1, 2 or 3 groups selected from $-CN$, halogen, nitro, $C_{1-6}alkyl$, $C_{1-4}haloalkyl$, $-OH$, $-OR^c$, $-NR^aR^b$, $-S(=O)_nR^c$, $-C(=O)Ra$, $-S(=O)NR^aR^b$, $-C(=O)NR^aR^a$, $-C(=O)OR^a$, $-NR^aC(=O)R^a$, $-OC(=O)R^a$, $B(OH)_2$, vicinal $-OCH_2CH_2O-$, vicinal $-OC_{1-2}haloalkylO-$, vicinal $-OCH_2O-$, vicinal $-CH_2OCH_2O-$, phenyl, benzyl and a 5- or 6-membered ring, saturated or unsaturated heterocycle containing 1, 2, 3 or 4 heteroatoms independently selected from N, O, or S;
- Y is CH_2 , $CHCH_3$, $S(=O)$ or $S(=O)_2$;

- 224 -

m is 1, 2 or 3;

n is 0, 1 or 2; and

- Het, unless otherwise defined, is a 5- or 6-membered ring, saturated or unsaturated heterocycle containing 1, 2, 3 or 4 heteroatoms independently selected from N, O, or S, and substituted by 0, 1, 2 or 3 substituents selected from halogen, $-(CH_2)_nR^d$, $C_{1-4}alkyl$, $-S(=O)_nR^c$, $-C(=O)R^a$, or $-S(=O)_2NR^aR^a$ vicinal $-OCH_2CH_2O-$, vicinal $-OC_{1-2}haloalkylO-$, vicinal $-OCH_2O-$, or vicinal $-CH_2OCH_2O-$, $=O$, halogen, cyano, $-R^bOR^a$, $-R^bSR^a$, $-SR^a$, $-OR^a$, $C_{1-6}alkyl$, $C_{1-6}haloalkyl$, $-CN$, nitro, $-OH$, $-NHR^a$, $-NR^a_2$, $-NHC(=O)R^a$, $N=NR^a$, $-C(=O)NR^aR^a$, $-C(=O)NR^aOR^a$, $-C(=O)NR^aR^bNR^aR^a$, $-C(=O)NR^aR^bOR^a$, $-C(=O)NR^aR^bS(=O)_nR^a$, $-C(=O)NR^aR^bHet$, $-C(=O)OR^a$, $-OC(=O)R^a$, $-C(=O)OR^bNR^aR^a$, $-C(=O)R^bNR^aR^a$, $-C(=NOR^a)R^a$, $-C(=NCN)R^a$, $-NR^aS(=O)_2R^a$, $-S(=O)_2NR^aR^bC(=O)NR^aR^a$, or $-S(=O)_2NR^aR^bC(=O)OR^a$;
- or a pharmaceutically acceptable salt thereof.

3. The compound as recited in Claim 1 wherein R^1 is $C_{1-4}alkyl$, $Het-C_{1-10}alkyl$, $R^d-C_{1-10}alkyl$ or $C_{1-10}alkyl$, or $-OH$ wherein it is optionally substituted by 1 or 2 substituents selected from halogen, $-OR^a$, $-NR^aR^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-OC(=O)C_{1-4}alkyl$ or $-NR^aC(=O)C_{1-4}alkyl$.
4. The compound as recited in Claim 2 wherein R^1 is $C_{1-4}alkyl$, $Het-C_{1-10}alkyl$, $R^d-C_{1-10}alkyl$ or $C_{1-10}alkyl$, or $-OH$ wherein it is optionally substituted by 1 or 2 substituents selected from halogen, $-OR^a$, $-NR^aR^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-OC(=O)C_{1-4}alkyl$ or $-NR^aC(=O)C_{1-4}alkyl$.
5. The compound as recited in Claim 1 wherein R^1 is $Het-C_{1-3}alkyl$, $R^d-(CH_2)_n-$ or $C_{1-6}alkyl$ that is substituted by 1 or 2 substituents selected from halogen, $-OR^a$, $-NR^aR^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-OC(=O)C_{1-4}alkyl$ or $-NR^aC(=O)C_{1-4}alkyl$.
6. The compound as recited in Claim 2 wherein R^1 is $Het-C_{1-3}alkyl$, $R^d-(CH_2)_n-$ or $C_{1-6}alkyl$ that is substituted by 1 or 2 substituents selected from halogen, $-OR^a$, $-NR^aR^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-OC(=O)C_{1-4}alkyl$ or $-NR^aC(=O)C_{1-4}alkyl$.

- 225 -

7. The compound as recited in Claim 1 wherein R^3 is represented by -Het, -Het-Het, R^5, R^5 -Het, -Het- R^5 , -Het-O- R^5 , -phenyl- R^5 or -phenyl-.
8. The compound as recited in Claim 2 wherein R^3 is represented by -Het, -Het-Het, R^5, R^5 -Het, -Het- R^5 , -Het-O- R^5 , -phenyl- R^5 or -phenyl-.
9. The compound as recited in Claim 1 where R^1 is represented by C_{1-6} alkyl, wherein it is optionally substituted by 1 or 2 substituents selected from halogen, $-OR^a$, $-NR^aR^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-OC(=O)C_{1-4}$ alkyl or $-NR^aC(=O)C_{1-4}$ alkyl.
10. The compound as recited in Claim 1 where R^1 is represented by C_{1-6} alkyl, wherein it is optionally substituted by 1 or 2 substituents selected from halogen, $-OR^a$, $-NR^aR^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-OC(=O)C_{1-4}$ alkyl or $-NR^aC(=O)C_{1-4}$ alkyl.
11. The compound as recited in Claim 1 wherein R^1 is methyl or ethyl optionally substituted with a substituted 5 or 6-membered heterocyclic ring.
12. The compound as recited in Claim 2 wherein R^1 is methyl or ethyl optionally substituted with a substituted 5 or 6-membered heterocyclic ring.
13. The compound as recited in Claim 11 wherein the heterocyclic is selected from imidazoyl, piperidinyl, methylpiperidinyl, or morpholinyl.
14. The compound as recited in Claim 12 wherein the heterocyclic is selected from imidazoyl, piperidinyl, methylpiperidinyl, or morpholinyl.
15. The compound as recited in Claim 1 wherein R^2 is $-C_{1-3}$ alkyl- $C(=O)R^a$; $-C_{1-3}$ alkyl- $C(=O)OR^a$; $-C_{1-3}$ alkyl- $C(=O)NR^aR^a$; $-C_{1-3}$ alkyl- $S(=O)_nR^c$; Het- C_{1-3} alkyl- R^5 - C_{1-3} alkyl-; or C_{1-12} alkyl substituted with 0, 1, 2 or 3 substituents selected from $-OH$, halogen, $-CN$, $-OR^a$, $-NR^aR^a$ and $-SR^c$.
16. The compound as recited in Claim 2 wherein R^2 is $-C_{1-3}$ alkyl- $C(=O)R^a$; $-C_{1-3}$ alkyl- $C(=O)OR^a$; $-C_{1-3}$ alkyl- $C(=O)NR^aR^a$; $-C_{1-3}$ alkyl- $S(=O)_nR^c$; Het- C_{1-3} alkyl-;

- 226 -

R^5 - C_{1-3} alkyl-; or C_{1-12} alkyl substituted with 0, 1, 2 or 3 substituents selected from -OH, halogen, -CN, -OR^a, -NR^aR^a and -SR^c.

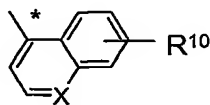
17. The compound as recited in Claim 1 wherein R² is Het- C_{1-3} alkyl-; R^5 - C_{1-3} alkyl-; C_{1-6} alkyl substituted with 0, 1 or 2 substituents selected from -OH, halogen, -CN, -OR^a, -NR^aR^a and SR^c.

18. The compound as recited in Claim 2 wherein R² is Het- C_{1-3} alkyl-; R^5 - C_{1-3} alkyl-; C_{1-6} alkyl substituted with 0, 1 or 2 substituents selected from -OH, halogen, -CN, -OR^a, -NR^aR^a and SR^c.

19. The compound as recited in Claim 17 wherein R² is -CH₂CH₂CH₃, -CH₂-cyclopropyl, -CH₂CH(CH₃)₂, -CH₂CH₂CH₂F, CH₂-cyclobutyl, -CH₂C(CH₃)₃, -CH₂CH₂CH(CH₃)₂, -CH₂CF₃, -CH₂-phenyl, -CH₂-phenyl, CH₂-isoxazolyl, -CH₂-S-phenyl, -CH₂-phenylcarboxyl, or -CH₂SCF₃.

20. The compound as recited in Claim 18 wherein R² is -CH₂CH₂CH₃, -CH₂-cyclopropyl, -CH₂CH(CH₃)₂, -CH₂CH₂CH₂F, CH₂-cyclobutyl, -CH₂C(CH₃)₃, -CH₂CH₂CH(CH₃)₂, -CH₂CF₃, -CH₂-phenyl, -CH₂-phenyl, CH₂-isoxazolyl, -CH₂-S-phenyl, -CH₂-phenylcarboxyl, or -CH₂SCF₃.

21. The compound as recited in Claim 1 wherein R³ is represented by Formula (i):

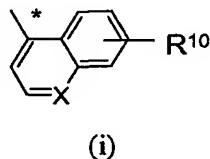


(i)

wherein * is the location where (i) is attached to Y, R¹¹ is optionally substituted alkyl, optionally substituted -S(=O)NR^aR^a or S(=O)_n, wherein n = 1 or 2 and wherein X is represented by C or N and Y is represented by C, N, S or O and wherein R¹⁰ is, at any position on the bicyclic ring, H, optionally substituted C_{1-6} alkyl, halogen, -CN, nitro, -CF₃, or -S(=O)₂CH₃.

- 227 -

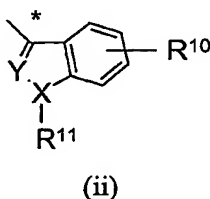
22. The compound as recited in Claim 2 wherein R^3 is represented by Formula (i):



5 wherein * is the location where (i) is attached to Y, R^{11} is optionally substituted alkyl, optionally substituted $-S(=O)NR^aR^a$ or $S(=O)_n$, wherein $n = 1$ or 2 and wherein X is represented by C or N and Y is represented by C, N, S or O and wherein R^{10} is, at any position on the bicyclic ring, H, optionally substituted C_{1-6} alkyl, halogen, -CN, nitro, $-CF_3$, or $-S(=O)_2CH_3$.

10

23. The compound as recited in Claim 1 wherein R^3 is represented by Formula (ii):

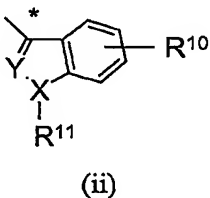


15

wherein * is the location where (ii) is attached to Y, wherein R^{11} is optionally substituted alkyl, optionally substituted $-S(=O)NR^aR^a$ or $S(=O)_n$, wherein $n = 1$ or 2 and wherein X and Y are independently represented by C, N, S, or O wherein X and Y are not simultaneously C, S, or O C and wherein X and Y are not S and O respectively or vice versa and wherein R^{10} is, at any position on the bicyclic ring, H, optionally substituted C_{1-6} alkyl, halogen, -CN, nitro, $-CF_3$, or $-S(=O)_2CH_3$.

20

24. The compound as recited in Claim 1 wherein R^3 is represented by Formula (ii):



25

- 228 -

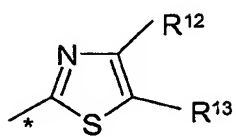
wherein * is the location where (ii) is attached to Y, wherein R¹¹ is optionally substituted alkyl, optionally substituted -S(=O)NR^aR^a or S(=O)_n, wherein n = 1 or 2 and wherein X and Y are independently represented by C, N, S, or O wherein X and Y are not simultaneously C, S, or O C and wherein X and Y are not S and O respectively or vice versa and wherein R¹⁰ is,
 5 at any position on the bicyclic ring, H, optionally substituted C₁₋₆alkyl, halogen, -CN, nitro, CF₃, or -S(=O)₂CH₃.

25. The compound as recited in Claim 2 wherein R⁴ is -(CH₂)_nphenyl, wherein the phenyl is substituted by 0, 1, 2 or 3 groups selected from -CN, nitro, C₁₋₆alkyl, halogen, C₁₋₄haloalkyl,
 10 -OH, -OR^c, -NR^aR^a, -S(=O)_nR^c, -C(=O)NR^aR^a, -C(=O)OR^a, -NR^aC(=O)R^a, -OC(=O)R^a, B(OH)₂, vicinal -OCH₂CH₂O-, vicinal -OC₁₋₂haloalkylO-, vicinal -OCH₂O-, vicinal -CH₂OCH₂O-, phenyl or benzyl.

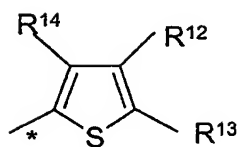
26. The compound as recited in Claim 2 wherein R⁴ is a saturated or unsaturated 5- or
 15 6-membered heterocyclic ring, containing 1, 2, 3 or 4 heteroatoms independently selected from N, O, or S, wherein the not more than one of the heteroatoms is S or O, and the ring is substituted by 0, 1 or 2 groups selected from -CN, nitro, C₁₋₆alkyl, C₁₋₄haloalkyl, -OH, -OR^c, -NR^aR^a, -S(=O)_nR^c, -S(=O)₂NR^a, -C(=O)NR^aR^a, -C(=O)OR^a, -NR^aC(=O)R^a, -OC(=O)R^a, B(OH)₂, vicinal -OCH₂CH₂O-, vicinal -OC₁₋₂haloalkylO-, vicinal -OCH₂O-, vicinal
 20 -CH₂OCH₂O-, phenyl or benzyl.

27. A compound as recited in Claim 1 wherein R⁴ is represented by formulas a, b, c, d, e, f, g, h, i, j, k l, m or n:

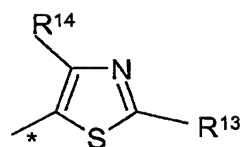
- 229 -



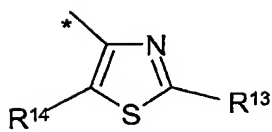
(a)



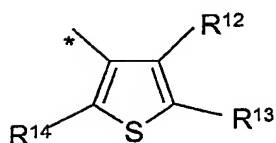
(b)



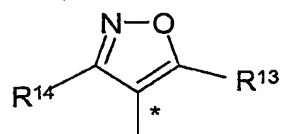
(c)



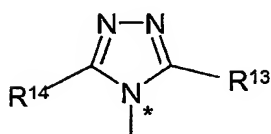
(d)



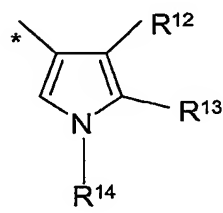
(e)



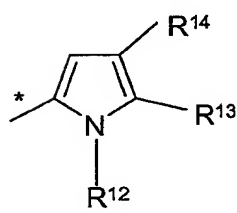
(f)



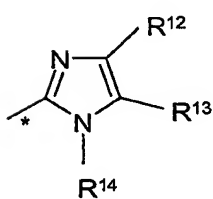
(g)



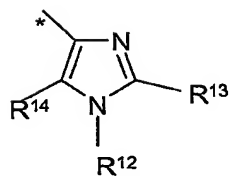
(h)



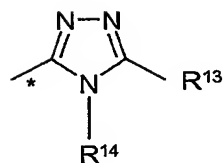
(i)



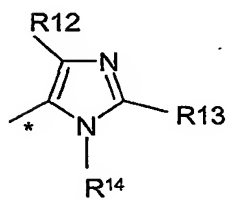
(j)



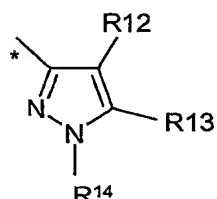
(k)



(l)



(m)

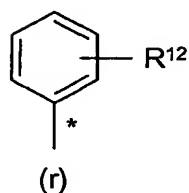
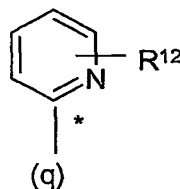
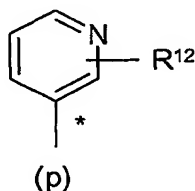
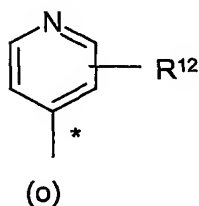


(n)

- 230 -

- wherein * is the location wherein R^4 is attached to the ring system and wherein wherein R^{12} , R^{13} and R^{14} are each independently represented by H, C_{1-6} alkyl, -CN, $-NR^aR^a$, -nitro, $-C(=O)R^a$, $-C(=O)NR^a$, $-C(=O)NR^aR^a$, $-C(=O)NR^aS(=O)_2R^a$, $-C(=O)NR^a$ -Het, -
- 5 $C(=O)NR^aN$, $-C(=O)NR^aNR^a$, $-C(=O)NR^aR^bNR^a_2$, $-C(=O)NR^aR^bNR^aR^a$, $-C(=O)NR^aR^bOR^a$, $-C(=O)NR^aR^bS(=O)_2R^a$, $-C(=O)NR^aR^b$ Het- $C(=O)NR^aO$, $-C(=O)NR^aOR^a$, $-C(=O)NOR^a$, $-C(=O)R^bNR^a$, $-C(=O)R^aN_2R^a$, $-C(=O)R^bNR^aR^a$, $-C(NOR^a)R^a$, $-C(=NCN)R^a$, $-C(=O)OR^a$, $-C(=O)OR^bNR^a$, $-C(=O)OR^bNR^aR^a$, $-C(=O)R^a$, $-C(=O)OR^bNR^aR^a$, $-OC(=O)R^a$, $-C(=O)R^a$ - SR^a , $=S$, $-NC(=O)R^a$, $-NC(=O)OR^a$, $-NS(=O)_2R^aR^b$, $-NR^bS(=O)_2R^a$, $C(=NO)R^a$, $-C(=NOR^a)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^a$, $-S(=O)_2NR^aR^a$, $-S(=O)_2NR^bC(=O)NR^aR^a$, $-S(=O)_2NR^aR^bC(=O)OR^a$, $-S(=O)_2NR^aC(=O)O$, or $-C(=NCN)R^a$.
- 10

28. A compound as recited in Claim 15 wherein R^4 is represented by formulas o-r as follows:



- 20 wherein * is the location wherein R^4 is attached to the ring system and wherein wherein R^{12} , R^{13} and R^{14} are each independently represented by H, C_{1-6} alkyl, -CN, $-NR^aR^a$, -nitro, $-C(=O)R^a$, $-C(=O)NR^a$, $-C(=O)NR^aR^a$, $-C(=O)NR^aS(=O)_2R^a$, $-C(=O)NR^a$ -Het, $-C(=O)NR^aN$, $-C(=O)NR^aNR^a$, $-C(=O)NR^aR^bNR^a_2$, $-C(=O)NR^aR^bNR^aR^a$, $-C(=O)NR^aR^bOR^a$, $-C(=O)NR^aR^bS(=O)_2R^a$, $-C(=O)NR^aR^b$ Het- $C(=O)NR^aO$, $-C(=O)NR^aOR^a$, $-C(=O)NOR^a$, $-C(=O)R^bNR^a$, $-C(=O)R^aN_2R^a$, $-C(=O)R^bNR^aR^a$, $-C(NOR^a)R^a$, $-C(=NCN)R^a$, $-C(=O)OR^a$, -
- 25

- 231 -

$C(=O)OR^bNR^a$, $-C(=O)OR^bNR^aR^a$, $-C(=O)R^a$, $-C(=O)OR^bNR^aR^a$, $-OC(=O)R^a$, $-C(=O)R^a-$
 SR^a , $=S$, $-NC(=O)R^a$, $-NC(=O)OR^a$, $-NS(=O)_2R^aR^b$, $-NR^bS(=O)_2R^a$, $C(=NO)R^a$, $-C(=NOR^a)$
 R^a , $-S(=O)_2R^a$, $-S(=O)_2NR^a$, $-S(=O)_2NR^aR^a$, $-S(=O)_2NR^bC(=O)NR^aR^a$, $-$
 $S(=O)_2NR^aR^bC(=O)OR^a$, $-S(=O)_2NR^aC(=O)O-$ or $-C(=NCN)R^a$.

5

29. The manufacture of a medicament for the treatment or prophylaxis of H. Pylori infection comprising a compound according to any one of Claims 1-28.

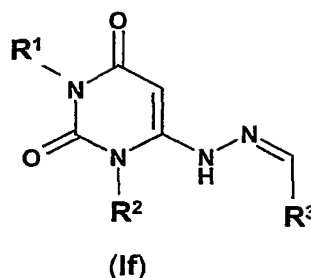
30. The use of a compound according to any one of Claims 1-28 for the treatment or
10 prophylaxis of H. Pylori infection.

31. A pharmaceutical composition for the treatment or prophylaxis of H. Pylori infection, comprising:

15 a therapeutically-effective amount of a compound according to any one of Claims 1-28; and
a pharmaceutically-acceptable diluent or carrier.

- 232 -

32. A compound of Formula (If):



5

R^1 is H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted cycloalkynyl, optionally substituted aryl, optionally substituted alkoxy, amino, or optionally substituted heterocycle;

R^2 is H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted cycloalkynyl, optionally substituted aryl, optionally substituted alkoxy, amino, or optionally substituted heterocycle;

R^3 is a monocyclic or bicyclic, saturated or unsaturated, ring system comprising 0, 1, 2 or 3 of heteroatoms independently selected from N, O, or S, the ring being substituted by 0, 1, 2 or 3 substituents selected from =O, halogen, $-OR^a$, C_{1-6} alkyl, C_{1-6} haloalkyl, -CN, nitro, , $-S(=O)_nR^c$, $-O(CH_2)_mHet$, $-O(CH_2)_mC(=O)Het$, $-O(CH_2)_mC(=O)NR^aR^a$, $-O(CH_2)_mC(=O)OR^a$, $-O(CH_2)_mNR^aR^a$, $-O(CH_2)_mOR^a$, $-S(CH_2)_mHet$, $-S(CH_2)_mC(=O)Het$, $-S(CH_2)_mC(=O)NR^aR^a$, $-S(CH_2)_mC(=O)OR^a$, $-S(CH_2)_mNR^aR^a$, $-S(CH_2)_mOR^a$, $-NHR^a$, $-NR^a_2$, $-NHC(=O)R^a$, $N=NR^a$, aminocarbonyl, phenyl or benzyl;

R^4 is C_{1-6} alkyl, $-NC_{1-6}$ alkyl, or $-N(C_{1-6}alkyl)_2$ wherein the C_{1-6} alkyl, $-NC_{1-6}$ alkyl, $-N(C_{1-6}alkyl)_2$ are substituted by 0, 1 or 2 substituents selected from R^a , OR^a , halogen or phenyl wherein R^4 is not $-(CH_2)_zCH_3$, $-(CH_2)_zCH_2OH$, $-(CH_2)_zCO_2H$, or $-(CH_2)_zCO_2C_{1-6}alkyl$ wherein z is 1, 2, 3, 4, 5, or 6;

R^5 is independently at each instance, phenyl substituted by 0, 1, 2, or 3 groups selected from halogen, C_{1-6} haloalkyl, $-OC_{1-6}$ haloalkyl, C_{1-6} alkyl, -CN, nitro, -OH, $-OR^c$, $-S(=O)_nR^c$, $-O(CH_2)_mHet$, $-O(CH_2)_mC(=O)Het$, $-O(CH_2)_mC(=O)NR^aR^a$, $-O(CH_2)_mC(=O)OR^a$,

- 233 -

-O(CH₂)_mNR^aR^a, -O(CH₂)_mOR^a, -S(CH₂)_mHet, -S(CH₂)_mC(=O)Het, -S(CH₂)_mC(=O)NR^aR^a,
 -S(CH₂)_mC(=O)OR^a, -S(CH₂)_mNR^aR^a, -S(CH₂)_mOR^a, -R^bOR^a, -SR^a, -C(=O)NR^aR^a, -
 C(=O)NR^aOR^a, -C(=O)NR^aR^bNR^aR^a, -C(=O)NR^aR^bOR^a, -C(=O)NR^aR^bS(=O)_nR^a, -
 C(=O)NR^aR^bHet, -C(=O)OR^a, -OC(=O)R^a, -C(=O)OR^bNR^aR^a, -C(=O)R^a, -C(=O)R^bNR^aR^a, -
 5 C(=NOR^a)R^a, -C(=NCN)R^a, -S(=O)₂NR^aR^a, -NR^aS(=O)₂R^a, -S(=O)₂NR^aR^bC(=O)NR^aR^a, or -
 S(=O)₂NR^aR^bC(=O)OR^a;

R^a is, independently at each instance, H, C₁₋₆alkyl, -C(=O)C₁₋₄alkyl, C₁₋₄haloalkyl, -
 (CH₂)_q-, phenyl, benzyl, or 5 or 6-membered ring, saturated or unsaturated heterocycle
 containing 1, 2, 3, or 4 heteroatoms independently selected from N, O or S and wherein q is 0,
 10 1, 2, 3, 4, 5 or 6;

R^b is, independently at each instance C₁₋₆alkyl, -C(=O)C₁₋₄alkyl, C₁₋₄haloalkyl, -
 (CH₂)_q-, phenyl, benzyl, or 5 or 6-membered ring, saturated or unsaturated heterocycle
 containing 1, 2, 3, or 4 heteroatoms independently selected from N, O or S and wherein q is
 0, 1, 2, 3, 4, 5 or 6;

15 R^c is C₁₋₆alkyl, C₁₋₄haloalkyl, phenyl or benzyl;

R^d is phenyl substituted by 0, 1, 2 or 3 groups selected from -CN, halogen, nitro,
 C₁₋₆alkyl, C₁₋₄haloalkyl, -OH, -OR^c, -NR^aR^b, -S(=O)_nR^c, -C(=O)R^a, -S(=O)NR^aR^b,
 -C(=O)NR^aR^a, -C(=O)OR^a, -NR^aC(=O)R^a, -OC(=O)R^a, B(OH)₂, vicinal -OCH₂CH₂O-,
 vicinal -OC₁₋₂haloalkylO-, vicinal -OCH₂O-, vicinal -CH₂OCH₂O-, phenyl, benzyl and a 5- or
 20 6-membered ring, saturated or unsaturated heterocycle containing 1, 2, 3 or 4 heteroatoms
 independently selected from N, O, or S;

Y is CH₂, CHCH₃, S(=O) or S(=O)₂;

m is 1, 2 or 3;

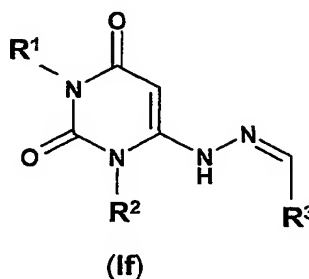
n is 0, 1 or 2; and

25 Het, unless otherwise defined, is a 5- or 6-membered ring, saturated or unsaturated
 heterocycle containing 1, 2, 3 or 4 heteroatoms independently selected from N, O, or S, and
 substituted by 0, 1, 2 or 3 substituents selected from halogen, -(CH₂)_nR^d, C₁₋₄alkyl, -S(=O)_nR^c,
 -C(=O)R^a, or -S(=O)₂NR^aR^a vicinal -OCH₂CH₂O-, vicinal -OC₁₋₂haloalkylO-, vicinal
 -OCH₂O-, or vicinal -CH₂OCH₂O-, =O, halogen, cyano, -R^bOR^a, -R^bSR^a, -SR^a, -OR^a,
 30 C₁₋₆alkyl, C₁₋₆haloalkyl, -CN, nitro, -OH, -NHR^a, -NR^a₂, -NHC(=O)R^a, N=NR^a, -
 C(=O)NR^aR^a, -C(=O)NR^aOR^a, -C(=O)NR^aR^bNR^aR^a, -C(=O)NR^aR^bOR^a, -
 C(=O)NR^aR^bS(=O)_nR^a, -C(=O)NR^aR^bHet, -C(=O)OR^a, -OC(=O)R^a, -C(=O)OR^bNR^aR^a, -

- 234 -

$C(=O)R^bNR^aR^a$, $-C(=NOR^a)R^a$, $-C(=NCN)R^a$, $-NR^aS(=O)_2R^a$, $-S(=O)_2NR^aR^bC(=O)NR^aR^a$, or $-S(=O)_2NR^aR^bC(=O)OR^a$.

5 33. A compound of Formula (If):



10 R^1 is H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted cycloalkynyl, optionally substituted aryl, optionally substituted alkoxy, amino, or optionally substituted heterocycle;

15 R^2 is H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted cycloalkynyl, optionally substituted aryl, optionally substituted alkoxy, amino, or optionally substituted heterocycle;

20 R^3 is a monocyclic or bicyclic, saturated or unsaturated, ring system comprising 0, 1, 2 or 3 of heteroatoms independently selected from N, O, or S, the ring being substituted by 0, 1, 2 or 3 substituents selected from $=O$, halogen, $-OR^a$, C_{1-6} alkyl, C_{1-6} haloalkyl, $-CN$, nitro, $-S(=O)_nR^c$, $-O(CH_2)_mHet$, $-O(CH_2)_mC(=O)Het$, $-O(CH_2)_mC(=O)NR^aR^a$, $-O(CH_2)_mC(=O)OR^a$, $-O(CH_2)_mNR^aR^a$, $-O(CH_2)_mOR^a$, $-S(CH_2)_mHet$, $-S(CH_2)_mC(=O)Het$, $-S(CH_2)_mC(=O)NR^aR^a$, $-S(CH_2)_mC(=O)OR^a$, $-S(CH_2)_mNR^aR^a$, $-S(CH_2)_mOR^a$, $-NHR^a$, $-NR^a_2$, $-NHC(=O)R^a$, $N=NR^a$, aminocarbonyl, phenyl or benzyl;

25 R^4 is $-(CH_2)_nphenyl-Het$, $-(CH_2)_nR^d$, $-Het$, $-Het-Het$, R^5 , $-R^5-Het$, $-Het-R^5$, $-Het-O-R^5$, $-phenyl-R^5$ or $-phenyl-OR^5$ or a monocyclic or bicyclic, saturated or unsaturated, ring system, or a vicinal-fused derivative thereof, which may contain from 5 to 12, preferably 5 to 10, ring atoms, 0, 1, 2, 3 or 4 of which are heteroatoms independently selected from N, O, or S, the

- 235 -

- ring system being substituted by 0, 1, 2 or 3 substituents selected from B(OH)₂, vicinal -OCH₂CH₂O-, vicinal -OC₁₋₂haloalkylO-, vicinal -OCH₂O-, vicinal -CH₂OCH₂O-, =O, halogen, -R^bOR^a, -SR^a, -OR^a, C₁₋₆alkyl, C₁₋₆haloalkyl, -CN, -S(=O)_nR^c, -O(CH₂)_mHet, -O(CH₂)_mC(=O)Het, -O(CH₂)_mC(=O)NR^aR^a, -O(CH₂)_mC(=O)OR^a, -O(CH₂)_mNR^aR^a, -
- 5 O(CH₂)_mOR^a, -S(CH₂)_mHet, -S(CH₂)_mC(=O)Het, -S(CH₂)_mC(=O)NR^aR^a, -S(CH₂)_mC(=O)OR^a, -S(CH₂)_mNR^aR^a, -S(CH₂)_mOR^a, -NHR^a, -NR^a₂, -NHC(=O)R^a, N=NR^a, NO₂, -C(=O)NR^aR^a, -C(=O)NR^aOR^a, -C(=O)NR^aR^bNR^aR^a, -C(=O)NR^aR^bOR^a, -C(=O)NR^aR^bS(=O)_nR^a, -C(=O)NR^aR^bHet, -C(=O)OR^a, -OC(=O)R^a, -C(=O)OR^bNR^aR^a, -C(=O)R^a, -C(=O)R^bNR^aR^a, -C(=NOR^a)R^a, -C(=NCN)R^a, -S(=O)₂NR^aR^a, -NR^aS(=O)₂R^a, -
- 10 S(=O)₂NR^aR^bC(=O)NR^aR^a, -S(=O)₂NR^aR^bC(=O)OR^a, aminocarbonyl, phenyl or benzyl;
- R⁵ is independently at each instance, phenyl substituted by 0, 1, 2, or 3 groups selected from halogen, C₁₋₆haloalkyl, -OC₁₋₆haloalkyl, C₁₋₆alkyl, -CN, nitro, -OH, -OR^c, -S(=O)_nR^c, -O(CH₂)_mHet, -O(CH₂)_mC(=O)Het, -O(CH₂)_mC(=O)NR^aR^a, -O(CH₂)_mC(=O)OR^a, -O(CH₂)_mNR^aR^a, -O(CH₂)_mOR^a, -S(CH₂)_mHet, -S(CH₂)_mC(=O)Het, -S(CH₂)_mC(=O)NR^aR^a, -
- 15 -S(CH₂)_mC(=O)OR^a, -S(CH₂)_mNR^aR^a, -S(CH₂)_mOR^a, -R^bOR^a, -SR^a, -C(=O)NR^aR^a, -C(=O)NR^aOR^a, -C(=O)NR^aR^bNR^aR^a, -C(=O)NR^aR^bOR^a, -C(=O)NR^aR^bS(=O)_nR^a, -C(=O)NR^aR^bHet, -C(=O)OR^a, -OC(=O)R^a, -C(=O)OR^bNR^aR^a, -C(=O)R^a, -C(=O)R^bNR^aR^a, -C(=NOR^a)R^a, -C(=NCN)R^a, -S(=O)₂NR^aR^a, -NR^aS(=O)₂R^a, -S(=O)₂NR^aR^bC(=O)NR^aR^a, or -S(=O)₂NR^aR^bC(=O)OR^a;
- 20 R^a is, independently at each instance, H, C₁₋₆alkyl, -C(=O)C₁₋₄alkyl, C₁₋₄haloalkyl, - (CH₂)_q-, phenyl, benzyl, or 5 or 6-membered ring, saturated or unsaturated heterocycle containing 1, 2, 3, or 4 heteroatoms independently selected from N, O or S and wherein q is 0, 1, 2, 3, 4, 5 or 6;
- R^b is, independently at each instance C₁₋₆alkyl, -C(=O)C₁₋₄alkyl, C₁₋₄haloalkyl, -
- 25 (CH₂)_q-, phenyl, benzyl, or 5 or 6-membered ring, saturated or unsaturated heterocycle containing 1, 2, 3, or 4 heteroatoms independently selected from N, O or S and wherein q is 0, 1, 2, 3, 4, 5 or 6;
- R^c is C₁₋₆alkyl, C₁₋₄haloalkyl, phenyl or benzyl;
- R^d is phenyl substituted by 0, 1, 2 or 3 groups selected from -CN, halogen, nitro,
- 30 C₁₋₆alkyl, C₁₋₄haloalkyl, -OH, -OR^c, -NR^aR^b, -S(=O)_nR^c, -C(=O)Ra, -S(=O)NR^aR^b, -C(=O)NR^aR^a, -C(=O)OR^a, -NR^aC(=O)R^a, -OC(=O)R^a, B(OH)₂, vicinal -OCH₂CH₂O-, vicinal -OC₁₋₂haloalkylO-, vicinal -OCH₂O-, vicinal -CH₂OCH₂O-, phenyl, benzyl and a 5- or

- 236 -

6-membered ring, saturated or unsaturated heterocycle containing 1, 2, 3 or 4 heteroatoms independently selected from N, O, or S;

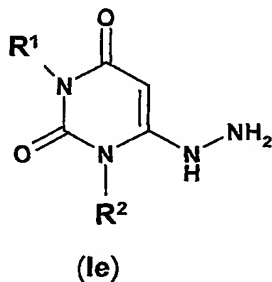
Y is CH₂, CHCH₃, S(=O) or S(=O)₂;

m is 1, 2 or 3;

5 n is 0, 1 or 2; and

Het, unless otherwise defined, is a 5- or 6-membered ring, saturated or unsaturated heterocycle containing 1, 2, 3 or 4 heteroatoms independently selected from N, O, or S, and substituted by 0, 1, 2 or 3 substituents selected from halogen, -(CH₂)_nR^d, C₁₋₄alkyl, -S(=O)_nR^c, -C(=O)R^a, or -S(=O)₂NR^aR^a vicinal -OCH₂CH₂O-, vicinal -OC₁₋₂haloalkylO-, vicinal
 10 -OCH₂O-, or vicinal -CH₂OCH₂O-, =O, halogen, cyano, -R^bOR^a, -R^bSR^a, -SR^a, -OR^a, C₁₋₆alkyl, C₁₋₆haloalkyl, -CN, nitro, -OH, -NHR^a, -NR^a₂, -NHC(=O)R^a, N=NR^a, -C(=O)NR^aR^a, -C(=O)NR^aOR^a, -C(=O)NR^aR^bNR^aR^a, -C(=O)NR^aR^bOR^a, -C(=O)NR^aR^bS(=O)_nR^a, -C(=O)NR^aR^bHet, -C(=O)OR^a, -OC(=O)R^a, -C(=O)OR^bNR^aR^a, -C(=O)R^bNR^aR^a, -C(=NOR^a)R^a, -C(=NCN)R^a, -NR^aS(=O)₂R^a, -S(=O)₂NR^aR^bC(=O)NR^aR^a, or
 15 -S(=O)₂NR^aR^bC(=O)OR^a.

34. A process for preparing a compound Formula If recited in Claim 32 comprising reacting a compound of Formula (Ie):



20

with R³-CHO in methanol.

35. A process for preparing a compound of Formula I recited in Claim 1 by reacting
 25 compound with R⁴-CHO in a solvent.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 02/01303

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 487/04, A61K 31/519, A61P 1/04
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D, A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CHEM. ABS DATA, EPO-INTERNAL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	STN International, file CAPLUS, CAPLUS accession no. 1977:468272, Document no. 87:68272, Yoneda, Fumio et al: "Synthesis of pyrazolo(3,4-d)pyrimidines by intramolecular cycloaddition of azahexatrienes"; & J. Chem. Soc., Perkin Trans. 1 (1977), (7), 765-7 --	2,4,8,10,32, 33
A	PEDIATRIC RESEARCH, Volume 40, no. 3, 1996, Günther Schimpl et al: "Allopurinol Reduces Bacterial Translocation, Intestinal Mucosal Lipid Peroxidation, and Neutrophil-Derived Myeloperoxidase Activity in Chronic Portal Hypertensive and Common Bile Duct-Ligated Growing Rats", page 422 - page 428 --	1-31

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

2 October 2002

Date of mailing of the international search report

04-10-2002

Name and mailing address of the ISA/
Swedish Patent Office
Box 5055, S-102 42 STOCKHOLM
Facsimile No. +46 8 666 02 86

Authorized officer

Eva Johansson/EÖ
Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 02/01303

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Arch Microbiol, Volume 168, 1997, George L. Mendz et al: "Purine metabolism and the microaerophily of Helicobacter pylori", page 448 - page 456 --	1-31
A	WO 9006116 A2 (HENNING BERLIN GMBH CHEMIE UND-PHARMAWERK), 14 June 1990 (14.06.90) --	1-31
A	STN International, file CAPLUS, CAPLUS accession no. 1986:179711, Document no. 104:179711, Patel, Vikram S. et al: "Allopurinol absorption from different sites of the rat gastrointestinal tract"; & J. Pharm. Sci. (1986, 75(3), 275-7 -- -----	1-31

02/09/02

PCT/SE 02/01303

Form PCT/ISA/210 (patent family annex) (July 1998)